

Wellcome Witnesses
to Twentieth Century Medicine

**PEPTIC ULCER:
RISE AND FALL**

The transcript of a Witness Seminar held at the
Wellcome Institute for the History of Medicine,
London, on 12 May 2000

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INTRODUCTION

Peptic ulcer has unquestionably been a disease of the twentieth century. Rare before the end of the previous century, peptic ulcer became increasingly frequent, reaching a peak during the next 50 years and afflicting as many as 10 per cent of men. There were two types of peptic ulcer: gastric ulcer, which appeared to be due to damage to the lining of the stomach, and duodenal ulcer, which was associated with excessive acid secretion by the stomach. Such ulcers did not occur if there was atrophy of the gastric mucosa, when no acid is secreted by the stomach. The aetiology of peptic ulcer was fiercely debated. Not unnaturally, in those post-Freudian days, psychosomatic influences were for long thought to be the cause of peptic ulcer, stress being the major culprit. The complications of peptic ulcer were an important cause of death, severe haemorrhage being common and perforation, particularly of duodenal ulcers, being a frequent surgical emergency. Obstruction of the stomach by pyloric stenosis might also occur.

The treatment of many cases of peptic ulcer was undertaken by the GP. Antacids were the mainstay but in more severe cases hospitalization and 'medical' treatment with a wide range of bland diets or with milk drips prevailed (see pages 10, 53, 55–56). There were always such patients languishing in bed in hospital wards throughout the country. When such measures failed, as frequently they did, the only recourse was surgery. For many years gastroenterostomy (for example, pages 18, 29, 58–59, 110–111) was considered to be the mainstay of surgical treatment, until it became apparent that the procedure was often followed by stomal ulceration. Partial gastrectomy then came to enjoy strong support, until the complications of dumping syndrome (see pages 59 and 60) and nutritional deficiency brought such procedures into disrepute. Vagotomy had been introduced as a means of reducing acid secretion but gastric stasis often resulted, encouraging surgeons to combine vagotomy with pyloroplasty or gastroenterostomy to facilitate gastric emptying. Vagotomy, however, was often followed by troublesome diarrhoea.

As Dr John Ford¹ has reminded me, for the GP there were often difficulties in persuading surgeons to operate even when those practitioners knew that there might be unpleasant after-effects. Patients were expected to 'earn' their operations, by enduring years of unsuccessful 'medical' treatment. There was also the problem that many surgeons lost interest in the patients who developed complications, leaving the GP to deal the situation as best he could.

A totally new dimension to the treatment came with the introduction in the 1970s, by Sir James Black, of the H₂ receptor antagonists. Ulcers would now heal without

¹ Dr John Ford's comments are written in a letter to Dr Daphne Christie, 8 June 2002, and will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

recourse to surgery and remain healed if drug treatment was continued. These developments greatly reduced admissions to hospital as well as the workload of gastric surgeons. At the same time, enormous profits were earned by the pharmaceutical firms involved in H₂ receptor antagonist manufacture.

The aetiology of peptic ulcer, for so long a matter for whimsical speculation, was suddenly illuminated in the early 1980s through the discovery by Barry Marshall and his colleagues in Perth, Western Australia, that a microorganism adhering to the mucosa of the stomach and duodenum was of major importance. The organism, *Helicobacter pylori*, was cultured from biopsy specimens and, when introduced into his own stomach, Marshall produced extremely unpleasant dyspeptic symptoms, which were relieved by appropriate antibiotic treatment. Never in their wildest dreams would many gastroenterologists have imagined that peptic ulcer might be an infectious disease.

There remains, however, an enigma. The prevalence of peptic ulcer has fallen during the later decades of the twentieth century, irrespective of the introduction of effective treatment. This apparently spontaneous fall remains to be explained. Nevertheless, the discovery that peptic ulcer may be an infectious disease raises the question, posed by James LeFanu,² that there may be other diseases of unknown aetiology such as coronary arteriosclerosis and rheumatoid arthritis which may also have an infective origin.

Sir Christopher Booth
Wellcome Trust Centre for the History of Medicine at UCL

² See LeFanu J. (1999) *The Rise and Fall of Modern Medicine*. London: Little, Brown and Company, 382–389.

WITNESS SEMINARS: MEETINGS AND PUBLICATIONS¹

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among a number of other initiatives the format of Witness Seminars, used by the Institute of Contemporary British History to address issues of recent political history, was adopted, to promote interaction between these different groups, to emphasize the potential of working jointly, and to encourage the creation and deposit of archival sources for present and future use. In June 1999 the Governors of the Wellcome Trust decided that it would be appropriate for the Academic Unit to enjoy a more formal academic affiliation and turned the Unit into the Wellcome Trust Centre for the History of Medicine at University College London from 1 October 2000. The Wellcome Trust continues to fund the Witness Seminar programme via its support for the Centre.

The Witness Seminar is a particularly specialized form of oral history where several people associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held over 30 such meetings, most of which have been published, as listed in the table on pages v–vii.

Subjects for such meetings are usually proposed by, or through, members of the Programme Committee of the Group, and once an appropriate topic has been agreed, suitable participants are identified and invited. These inevitably lead to further contacts, and more suggestions of people to invite. As the organization of the meeting progresses, a flexible outline plan for the meeting is devised, usually with assistance from the meeting's chairman, and some participants are invited to 'set the ball rolling' on particular themes, by speaking for a short period of time to initiate and stimulate further discussion.

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is immediately sent to every participant. Each is asked to check their own contributions and to provide brief biographical details. The editors turn the transcript into readable text, and participants' minor corrections and comments are incorporated into that text, while biographical and bibliographical details are added as footnotes, as are more substantial comments and additional material provided by participants. The final scripts are then sent to every contributor, accompanied by forms assigning copyright to the Wellcome Trust. Copies of all additional correspondence received during the editorial process are deposited with the records of each meeting in Archives and Manuscripts, Wellcome Library, London.

¹ The following text also appears in the 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicine* published by the Wellcome Trust and the Wellcome Trust Centre for the History of Medicine at University College London.

As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the nonspecialist, the sense and significance of the events are understandable. Our aim is for the volumes that emerge from these meetings to inform those with a general interest in the history of modern medicine and medical science; to provide historians with new insights, fresh material for study, and further themes for research; and to emphasize to the participants that events of the recent past, of their own working lives, are of proper and necessary concern to historians.

Members of the Programme Committee of the History of Twentieth Century Medicine Group

The Group's activities are overseen by the Programme Committee, which includes professional historians of medicine, practising scientists and clinicians. The Programme Committee during 2001–02 comprised:

Dr Tilli Tansey – Historian of Modern Medical Science, Wellcome Trust Centre at UCL, and Chair

Sir Christopher Booth – Wellcome Trust Centre at UCL, former Director, Clinical Research Centre, Northwick Park Hospital, London

Dr Robert Bud – Head of Life and Environmental Sciences, Science Museum, London

Dr Daphne Christie – Senior Research Assistant, Wellcome Trust Centre at UCL and Organizing Secretary

Professor Hal Cook – Director, Wellcome Trust Centre at UCL

Dr Mark Jackson – Reader, Centre for Medical History, Exeter

Professor Ian McDonald – Harveian Librarian, Royal College of Physicians, London

Dr Jon Turney – Head of the Department of Science and Technology Studies, University College London

HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2003

- 1993** **Monoclonal antibodies¹**
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994** **The early history of renal transplantation**
Organizer: Dr Stephen Lock
- Pneumoconiosis of coal workers²**
Organizer: Dr E M Tansey
- 1995** **Self and non-self: a history of autoimmunity¹**
Organizers: Sir Christopher Booth and Dr E M Tansey
- Ashes to ashes: the history of smoking and health³**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Oral contraceptives**
Organizers: Dr Lara Marks and Dr E M Tansey
- Endogenous opiates¹**
Organizer: Dr E M Tansey
- 1996** **Committee on Safety of Drugs¹**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Making the body more transparent: the impact of nuclear magnetic resonance and magnetic resonance imaging⁴**
Organizer: Sir Christopher Booth
- 1997** **Research in General Practice⁴**
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice⁴**
Organizers: Dr David Healy and Dr E M Tansey
- The MRC Common Cold Unit⁴**
Organizers: Dr David Tyrrell and Dr E M Tansey
- The first heart transplant in the UK⁵**
Organizer: Professor Tom Treasure
- 1998** **Haemophilia: recent history of clinical management⁶**
Organizers: Professor Christine Lee and Dr E M Tansey
- Obstetric ultrasound: historical perspectives⁷**
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post penicillin antibiotics⁸**
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980⁹**
Organizers: Dr David Gordon and Dr E M Tansey

- 1999** **Intestinal absorption**¹⁰
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**¹¹
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**¹²
Organizers: Professor Osmund Reynolds and Dr E M Tansey
- British contributions to medicine in Africa after the Second World War**¹³
Organizers: Dr Mary Dobson, Dr Maureen Malowany,
Dr Gordon Cook and Dr E M Tansey
- 2000** **Childhood asthma, and beyond**¹⁴
Organizers: Dr Chris O'Callaghan and Dr Daphne Christie
- Peptic ulcer: rise and fall**¹⁵
Organizers: Sir Christopher Booth, Professor Roy Pounder and Dr E M Tansey
- Maternal care**¹⁶
Organizers: Dr Irvine Loudon and Dr Daphne Christie
- 2001** **Leukaemia**¹⁷
Organizers: Professor Sir David Weatherall, Professor John Goldman,
Sir Christopher Booth and Dr Daphne Christie
- The MRC Applied Psychology Unit**¹⁸
Organizers: Dr Geoff Bunn and Dr Daphne Christie
- Genetic testing**¹⁹
Organizers: Professor Doris Zallen and Dr Daphne Christie
- Foot and mouth disease**²⁰
Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin
- 2002** **Environmental toxicology: The legacy of silent spring**
Organizers: Dr Robert Flanagan and Dr Daphne Christie
- Cystic fibrosis**
Organizers: Dr James Littlewood and Dr Daphne Christie
- Innovation in pain management**
Organizers: Professor David Clark and Dr Daphne Christie
- 2003** **Thrombolysis**
Organizers: Mr Robert Arnott and Dr Daphne Christie
- Beyond the asylum: Anti-psychiatry and care in the community**
Organizers: Dr Mark Jackson and Dr Daphne Christie
- The Rhesus factor story**
Organizers: Professor Doris Zallen and Dr Daphne Christie

- ¹ Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) (1997) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust, 135pp.
- ² Hart, P D'Arcy, edited and annotated by Tansey E M. (1998) Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–1942). *Social History of Medicine* 11: 459–468.
- ³ Lock S P, Reynolds L A, Tansey E M. (eds) (1998) *Ashes to Ashes – The history of smoking and health*. Amsterdam: Rodopi B V, 228pp.
- ⁴ Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 2. London: The Wellcome Trust, 282pp.
- ⁵ Tansey E M, Reynolds L A. (eds) (1999) Early heart transplant surgery in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 3. London: The Wellcome Trust, 72pp.
- ⁶ Tansey E M, Christie D A. (eds) (1999) Haemophilia: Recent history of clinical management. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 4. London: The Wellcome Trust, 90pp.
- ⁷ Tansey E M, Christie D A. (eds) (2000) Looking at the unborn: Historical aspects of obstetric ultrasound. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 5. London: The Wellcome Trust, 80pp.
- ⁸ Tansey E M, Reynolds L A. (eds) (2000) Post penicillin antibiotics: From acceptance to resistance? *Wellcome Witnesses to Twentieth Century Medicine*, vol. 6. London: The Wellcome Trust, 71pp.
- ⁹ Reynolds L A, Tansey E M. (eds) (2000) Clinical research in Britain, 1950–1980. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 7. London: The Wellcome Trust, 74pp.
- ¹⁰ Christie D A, Tansey E M. (eds) (2000) Intestinal absorption. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 8. London: The Wellcome Trust, 81pp.
- ¹¹ Ness A R, Reynolds L A, Tansey E M. (eds) (2002) Population-based Research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 150pp.
- ¹² Christie D A, Tansey E M. (eds) (2001) Origins of neonatal intensive care in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 9. London: The Wellcome Trust Centre for the History of Medicine at UCL, 84pp.
- ¹³ Reynolds L A, Tansey E M. (eds) (2001) British contributions to medical research and education in Africa after the second world war. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp.
- ¹⁴ Reynolds L A, Tansey E M. (eds) (2001) Childhood asthma and beyond. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 11. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp.
- ¹⁵ Christie D A, Tansey E M. (eds) (2002) Peptic ulcer: Rise and fall. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 14. London: The Wellcome Trust Centre for the History of Medicine at UCL, 143pp.
- ¹⁶ Christie D A, Tansey E M. (eds) (2001) Maternal care. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 12. London: The Wellcome Trust Centre for the History of Medicine at UCL, 88pp.
- ¹⁷ Christie D A, Tansey E M. (eds) (2003) Leukaemia. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 15. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.
- ¹⁸ Reynolds L A, Tansey E M. (eds) (2003) The MRC Applied Psychology Unit. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 16. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.
- ¹⁹ Christie D A, Tansey E M. (eds) (2003) Genetic testing. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 17. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.
- ²⁰ Reynolds L A, Tansey E M. (eds) (2003) Foot and Mouth Disease: The 1967 outbreak and its aftermath. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press.

ACKNOWLEDGEMENTS

'Peptic Ulcer: Rise and fall' was suggested as a suitable topic for a Witness Seminar by Professor Roy Pounder. He provided many of the names of individuals to be invited, assisted us in planning the meeting, and deciding the topics to be discussed, and we are very grateful for his input. He was especially helpful during the editorial process and provided assistance with compiling the glossary. We are also grateful to him for his excellent chairing of the occasion. Sir Christopher Booth and Dr Tilli Tansey both assisted with the organization of the meeting; Dr John Ford kindly read the edited transcript for general sense and understandability, and offered suggestions for glossary terms; Professor Roy Pounder allowed us to reproduce a selection of his photographs here; Professors Langman and Wyllie also provided photographs as did Alan Humphries of Thackray Museum, Leeds, who provided the pictures of the gastroscopes. We are particularly grateful to Sir Christopher Booth for writing such a useful introduction to these published proceedings.

As with all our meetings, we depend a great deal on our colleagues at the Wellcome Trust to ensure their smooth running: the Audiovisual Department, the Medical Photographic Library and Mrs Tracy Tillotson; Ms Julie Wood, who has supervised the design and production of this volume, our indexer, Mrs Liza Furnival, our readers, Dr John Ford, Ms Lucy Moore and Mr Simon Reynolds, and to Mr Mark Krüger for bibliographic research. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Mrs Lois Reynolds assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Daphne Christie

Wellcome Trust Centre for the History of Medicine at UCL

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Edited by D A Christie and E M Tansey

PARTICIPANTS

Dr John Atherton	Dr Belinda Johnston
Dr Hugh Baron	Professor Roger Jones
Sir James Black	Mr Raymond Kirk
Dr Joseph N Blau	Professor Michael Langman
Sir Christopher Booth	Professor John Lennard-Jones
Mr Roger Celestin	Dr Robert Logan
Dr Nelson Coghill*	Professor Kenneth McColl
Dr Gerard Crean	Dr George Misiewicz
Dr Booth Danesh	Professor Timothy Northfield
Professor Graham Dockray	Professor Colm Ó'Moráin
Sir Richard Doll	Dr John Paulley
Dr Peter Down	Professor Roy Pounder (Chair)
Sir Patrick Forrest	Professor Robert Steiner
Professor Stewart Goodwin	Dr Tilli Tansey
Dr Jean Guy	Mr Frank Tovey
Professor Michael Hobsley	Dr David Tyrrell
Dr Peter Hunter	Dr John Wood

Others attending the meeting: Dr John Ford, Professor Christopher Hawkey, Dr Toine Pieters, Professor John Pickstone, Dr Andrew Seal, Dr Malcolm Segal, Professor Rodney Taylor

Apologies: Professor Anthony Axon, Dr Chandu Bardhan, Professor David Johnstone, Sir Andrew Kay, Professor Barry Marshall, Dr Ashley Price, Lord Turnberg of Cheadle

*Deceased 21 April 2002

Dr Tilli Tansey: Welcome to this Seminar on the rise and fall of peptic ulcer throughout the twentieth century. The History of Twentieth Century Medicine Group was established by the Wellcome Trust in 1990, to bring together clinicians, scientists, medical historians and others interested in the recent history of medicine and medical sciences. Over the past ten years we have devised a number of mechanisms to achieve this aim. A particularly successful one has been that of holding Witness Seminars. A witness seminar is a meeting to which we invite people who have been involved in a particular event, circumstance or discovery, to come together to discuss between themselves, to debate, agree and disagree about their reminiscences, about what happened, and why it happened.

Looking at the subject of today's meeting, peptic ulcers provide a very rich territory for historians to traverse. For some time Chris Booth and I have talked about organizing a meeting on this subject. We failed to do so. It has taken Roy Pounder's enthusiasm and energy to get this meeting off the ground and we are very grateful to him for taking the time and interest in helping to organize today's meeting. We are also particularly indebted to him for agreeing to chair the proceedings, and it is appropriate at this stage for me to hand the meeting over to him.

Professor Roy Pounder: Thank you very much, Tilli, for your kind introduction. Welcome everybody to what I hope will be a very, very enjoyable day. Peptic ulcer disease over the last 50 or 100 years is a quite extraordinary story. I think it is an inspiring story of successive advances: when we thought we had just got everything sorted out, then an even better solution arrived, and then a better solution, and then a better solution. So what we hope to do today is to get the people who were there to tell quite a lot of the stories about what happened: the various aspects of the developments – the wrong turns that were taken and the correct turns – so that we get a record of the history of peptic ulcer. And this is proudly or unashamedly a British meeting. I think that Britain has certainly fought above its weight, as far as peptic ulcer disease is concerned, over the last 50 years.

The layout of the meeting is in four sessions. The first session is about what happened 50 years ago and various ideas about aetiology of peptic ulcer disease. The second part is about the diagnosis of ulcer disease, the pathogenesis of peptic ulcer disease, and we will probably bring forward surgery into that session. We can then provide you with two knights: Sir Richard Doll and Sir James Black will start the next session, which will be about the medical treatment of peptic ulcer disease, and the introduction of clinical trials to the medical world through peptic ulcer disease. The final session is the thing that amazed us all, and that is to do with *Helicobacter pylori*. So that's the layout of the meeting and the first witness is Hugh Baron.

SESSION 1: 50 YEARS AGO, AND AETIOLOGY OF PEPTIC ULCER DISEASE

Dr Hugh Baron: The first known peptic ulcer was found recently in China in a corpse of 2200 years ago.¹ It has increased in frequency since then. But there is this gap of 2000 years since the Greeks started Western medicine, and conceived that abdominal pain could be due to an ulcer inside the stomach lining akin to ulcers they were familiar with on the rest of the body. The testing of this hypothesis could, of course, come only from necropsies from about the fifteenth century, when ulcers, first gastric, then in the eighteenth century duodenal, were recorded, and became commoner, and then later, less frequent in most age groups.²

I have been devoted to the study of ulcers since 1952, when Avery Jones taught me how little was known of this increasingly common disease, and Richard Doll, how to answer some of the questions by epidemiology, and others by placebo-controlled, clinical trials of medical treatments, then all useless except for bed rest and stopping smoking.

In 1958, back at the Middlesex, I chose ‘acid and ulcers’ for my research, because of the efficacy of half a century of acid-lowering operations. I soon learnt that English physicians were apathetic, indeed antipathetic to acid, probably because they too had suffered, as I had in 1949, ghastly gastric intubation and a gruel meal like a prisoner suffragette as a physiology class experiment. And partly because these test meals were part of the hocus pocus of private clinics in various countries, whereas real clinical science was cardiopulmonary, renal, certainly not hydrochloric acid. Yes, English physiologists, ever since Hunter, Prout, Edkins, Bayliss and Starling, were all acid pioneers and in the 1950s there were, for example, Rod Gregory in Liverpool and J N Hunt at Guy’s, but neither had clinical collaborators. Physicians like Atkinson, James, and Watkinson forsook acid for lack of encouragement, and Sircus and Card³ had to emigrate from England to Scotland to join John Bruce at his gastrointestinal combined medical/surgical unit at the Western in Edinburgh. They, and Andrew Kay in Glasgow, conceived the augmented histamine test; maximum acid output and parietal-cell mass, and thus revolutionized exocrinology.⁴ With my peak acid output results I formulated the hypersecretory pathophysiology of duodenal ulcer, with a threshold of 15-mmol hydrochloric acid per hour, below which one could not get a

¹ Wu Z. (1980) Study of the ancient corpse of the Western Han dynasty unearthed from tomb no. 168 on Phoenix Hill at Jiangling County. *Medical Bulletin of Wuhan Medical College* 1: 1–12.

² Baron J H. (2000) Peptic ulcer. *Mount Sinai Journal of Medicine* 67: 58–62.

³ See, for example, Card W L. (1952) Peptic ulcer – aetiology, in Jones F A. (ed.) *Modern Trends in Gastroenterology*. London: Butterworths, 380–388. Sircus W. (1979) The Andrew Melrose Lecture 1977, Part I. The enigma of peptic ulcer. *Scottish Medical Journal* 24: 31–37.

⁴ Kay A W. (1953) Effect of large doses of histamine on gastric secretion of HCl. An augmented histamine test. *British Medical Journal* ii: 77–80. See also page 62.

duodenal ulcer.⁵ The Medical Research Council sent me for a year to Mount Sinai in New York where by analogy I developed the maximal bicarbonate output of the pancreas. I came back as a lecturer and one evening after a Medical Research Society meeting I was approached by a mandarin from the Medical Research Council who asked me if, as a high flyer, I would like to become a tenured clinical investigator of the Medical Research Council. For a few seconds I was ecstatic with this offer but then heard, ‘We have decided that the future of gastroenterology lies in immunology, you will have to become an immunologist and give up all that acid nonsense’. I begged to differ and later the Medical Research Council effectively recommended against funding acid research.⁶ So I gave up an academic career for a clinical one, but fortunately I was able to join [Richard] Welbourn’s Department of Surgery at Hammersmith for the next 28 years with support from the Wellcome Trust and then from industry.

It is fair to say that English physicians and the British pharmaceutical industry continued to pooh-pooh acid until 1972, when Black’s H₂ receptor blockers,⁷ of which we shall hear later, changed the ulcer world for ever, and confirmed the threshold model – that a powerful enough acid inhibitor would heal any ulcer. Admittedly, we were still ignorant of ulcer pathogenesis, we shall hear about answers to those questions as well. My role was simply to speak about what happened 50 years ago, to supplement what I have published.

Sir Patrick Forrest: May I make one brief comment to recognize the contribution which Charles Code at the Mayo Clinic Rochester, Minnesota, made to academic surgery and gastrointestinal research in Britain. A Canadian, he had come to Britain to work with Sir Henry Dale in London, and felt indebted to this country. Recognizing the lack of research facilities in our medical schools after the Second World War, he arranged that whole successions of young surgeons and physicians in training were offered research facilities in his laboratory, many of whom were subsequently appointed to chairs in the UK. They included Richard Welbourn, Theo Schofield and Edgar Parry from Liverpool; Ross Mitchell, Alan Smith and David Ritchie from Edinburgh; Geoffrey Watkinson from Leeds; Reg Livingstone and Ivan Johnston from Belfast; Robert Shields, Bert Duthie and Bill Irvine from Glasgow; Brian Creamer from London; and myself from Dundee. It was this opportunity that stimulated the interest, if not the obsession, of British academic surgeons to conduct studies of gastric secretion in dogs.

Pounder: And that, unfortunately, is a trend that has stopped. The number of people – young gastroenterologists and young surgeons – going overseas is now very limited. Michael Langman is also going to talk about the early days.

⁵ Baron J H. (1963) Studies of basal and peak acid output with an augmented histamine test. *Gut* 4: 136–144. See also *idem* (1979) The discovery of gastric acid. *Gastroenterology* 76: 1056–1064.

⁶ A report followed a review conducted by Professor R A Gregory and Sir Andrew Watt Kay. See Medical Research Council Annual Report 1975–1976. (1976) *Physiological Systems and Disorders Board*. London: HMSO, 65. The MRC Gastroenterology Unit was due to close in 1977.

⁷ *op. cit.* note 125.

Professor Michael Langman: What I would like to do is talk a little bit about ideas. I went back to the volume of *Modern Trends in Gastro-enterology*,⁸ published in 1952, which was probably commissioned about 1949. There are two chapters there, one is on the endemiology of ulcer⁹ – I have to say a word that was unfamiliar to me – and I asked Richard Doll, who wrote the chapter, whether he invented the word because the disease was endemic. That chapter is essentially, I think, descriptive of the frequency of ulcer in different places, but doesn't attempt to look at individual factors on causation, although Richard himself had worked on familial factors and had already described the association with smoking.¹⁰ The next chapter was written by Wilfred Card,¹¹ and I now read out what was written early on. It says, 'The cause of peptic ulcer is the digestion by acid and pepsin of the oesophageal, gastric, duodenal or intestinal mucosa'. It's a highly trenchant statement, but it doesn't take you very far, it certainly doesn't as an epidemiologist. It then goes into a series of other particular factors, mucus, nutrition, blood supply and hormonal, to explain the difference between men and women. It rather misses the point of whether smoking is important, it's not mentioned. It was Mervin Susser in the 1960s who described the cohort phenomenon and the rise and then decline of peptic ulcer, which he was already recognizing towards the end of the 1950s.¹² It was Brian Billington in 1960–63 who described the gastric ulcer change in Australia and the first acceptance after Douthwaite and Lintott – in 1938, I think – that anti-inflammatories are important.¹³ I think it was Bill Summerskill in 1958 who pointed to the association of aspirin and gastric bleeding.¹⁴ So we are beginning to head towards at least one of the phenomena that are important, the anti-inflammatories. The other, of course, is infection. I remember Richard [Doll], when I was working for him, saying, 'I don't suppose this is infective?' We were discussing, I think, some possible viral aetiology discussed in the Scandinavian literature and I remember saying, 'No'. It was not long after that in Avery's unit we heard someone discuss gastric urease. The paper by Freisinger was published in *Gut* in about 1964.¹⁵ I remember thinking, 'This is very odd, there isn't one', but never asked the right question, that is, 'Is the enzyme present in something

⁸ Avery Jones F. (ed.) (1952) *Modern Trends in Gastro-enterology*. London: Butterworth & Co. (Publishers) Ltd.

⁹ Doll R. (1952) Peptic ulcer. Endemiology, in Avery Jones F. (ed.) op. cit. note 8, chapter 16. Section I, 361–379.

¹⁰ See Lock S P, Reynolds L A, Tansey E M. (eds) (1998) *Ashes to Ashes: The history of smoking and health*. Amsterdam: Rodopi B V.

¹¹ Card W. (1952) Peptic ulcer. Aetiology, in Avery Jones F. (ed.) op. cit. note 8, chapter 16. Section II, 380–398.

¹² Susser M, Stein Z. (1962) Civilisation and peptic ulcer. *Lancet* i: 115–119.

¹³ Douthwaite R H D, Lintott G A M. (1938) Gastroscopic observation of effect of aspirin on the stomach. *Lancet* ii: 1222–1225. A brief description of Lintott's work and early death from dysentery in 1941 are given in a letter from Dr John Poulley to Dr Tilli Tansey, 13 October 2000. Billington B P. (1960) The Australian gastric ulcer change: further observations. *Medical Journal of Australia* 47: 19–20.

¹⁴ Alvarez A S, Summerskill W H J. (1958) Gastrointestinal haemorrhage and salicylates. *Lancet* ii: 920–925. See also Duggan J M. (1965) The relationship between perforated peptic ulcer and aspirin ingestion. *Medical Journal of Australia* 2: 659–662. For a review, see, for example, John D J. (1975) Gastric mucosal damage by aspirin. *CRC Critical Reviews in Toxicology* 3: 317–344.

¹⁵ Freisinger F R. (1963) An antibody precipitating urease and its possible relation to gastric ulcer. *Gut* 4: 339–343.

(a bacterium) on the mucosa?’ But neither did anybody else. Others, I think, can talk more about *H. pylori*.

I can say a little bit more about anti-inflammatories, in which I continued to take an interest. It became plain while we were working on aspirin and gastrointestinal bleeding that other drugs, the non-steroidals, might be important, and it badly needed a proper epidemiological study, at least I thought so. So at that time, it must have been about the end of the 1970s, with Chris Hawkey we cobbled together an application to the Medical Research Council, one part of which was to look at the epidemiology of ulcer, which was my bit, and the other bit, to look at prostaglandins, which was his. The Medical Research Council accepted enthusiastically the prostaglandin side and said that my side wasn’t worth doing at all, and thereby missed looking at the commonest adverse effect of a serious nature ever described for any group of drugs at any time. Maybe they didn’t need to, because we got it funded, and we did the work anyway. So I think what we have seen from the early 1960s is a thread of some isolated observations; Brian Billington’s were important, and Susser’s on the cohort phenomenon were important.¹⁶ That moved us towards the fundamental changes that came in looking at infections, the relationship with smoking, and the advent of anti-inflammatories.

Sir Christopher Booth: Thinking back to 50 years ago, I honestly don’t think anybody had the foggiest idea of aetiology, and I don’t think Billington’s work or any of that made any impact on any of us who were working as clinicians at that time.

What I would really like to try to tease out is what people really thought was happening. The only people who have been much involved with ulcers, by say in 1945 until 1950, apart from Avery’s unit and Richard [Doll], were the group of Berkeley Moynihan. Moynihan had this completely fixed idea that ulcers were associated with acid.¹⁷ Acid was the key thing that mattered and he made that point throughout his life.

Looking back, I can remember working as a house surgeon with Patrick Forrest as my registrar, with Frank Brown in Dundee, we had a perforated duodenal ulcer virtually every emergency on-take day. You didn’t feel you had been on-take, unless you had a perforated ulcer. What was it that led to a situation at the beginning of the century when that was a rare disease and when ulcer itself was a rare disease, and yet by 1950 it was a scourge? If you read about that period in Hamilton Bailey’s *Textbook of Surgery*¹⁸ it just sets out the common nature of it, and also gives the rising prevalence of the disorder in Western communities, particularly in Britain, and for some reason in Glasgow. And what was it by 1950 that did that? What did people think?

¹⁶ op. cit. notes 12, 13 and 54.

¹⁷ Moynihan B. (1919) The diagnosis and treatment of chronic gastric ulcer. *British Medical Journal* ii: 765–769. *idem* (1923) *Two Lectures in Gastric and Duodenal Ulcer: A record of ten years experience*. Bristol: John Wright & Sons Ltd.

¹⁸ Bailey H, McNeill Love R J. (1952) *A Short Practice of Surgery*. 9th Edition. London: H K Lewis Ltd, 269–308.

Langman: There are two things: what did people think and what happened? Firstly, people's thinking was dominated by psychosomatic factors, stress, the possibility that it was something to do in a vague way with civilization, but didn't look a great deal outside for discrete factors that might have caused the disease to happen. Richard Doll might like to comment on this, because he was involved early on in occupational studies, smoking studies and in studies of families.

Sir Richard Doll: Yes. I would like to say something about psychosomatic factors. Richard Asher, who was working at the same hospital as I was at the time, the Central Middlesex, gave me an article to read about duodenal ulcer and its cause by psychological stress.¹⁹ And he said, 'Do you think that's a fair account of what people think?' and I said, 'Well, it's a bit stilted language, Richard, but yes, it's a perfectly fair account'. He said, 'Actually, it was written in 1850 about general paralysis of the insane. And I merely substituted peptic ulcer for general paralysis of the insane'. I suppose at one time I did contribute to the idea that stress might play a part, because in our survey of ulcers in the population we did find that there was a relatively high incidence in foremen in factories, rather than other workers, and this was possibly due, we suggested, to the responsibilities that they had.²⁰ The only research I tried to do to test whether stress had any effect was something that I regret I never published. We drew up a list of all the things that we thought might be most worrying to people, like loss of job, members of their family dying, divorce, a whole list of some dozen objectively determinable factors that might cause stress. I think Michael [Langman] was with us at the time – no, it was with Donald Kellock. We then looked at how often these events had occurred prior to a patient's admission to hospital for haematemesis, which was frequently described as due to stress on top of an ulcer, and how often they had occurred before the admission of patients in a control group. We found that the proportion was exactly the same in both groups.

Pounder: A similar study took place in Australia where they looked at the life events of people with duodenal ulcer disease.²¹ They then went through the electoral register to look at the neighbours and asked them about their life events – and life was equally awful for the neighbours. There was a study that measured stress that reported that the life events are the same, but ulcer patients *suffer* more because of them.²² I think, Dr Paulley, you have a particular interest in stress and the causation of ulcer disease?

¹⁹ See Asher R. (ed.) (1972) *Talking Sense*. Bath: Pitman Medical, 43–53, in particular page 46.

²⁰ Doll R, Jones F A. (1951) *Occupational Factors in the Aetiology of Gastric and Duodenal Ulcer. With an estimate of the incidence in the general population*. London: HMSO. MRC Special Report Series, no. 276. Dunn J P, Cobb S. (1962) Frequency of peptic ulcer among executives, craftsmen and foremen. *Journal of Occupational Medicine* 4: 343–348.

²¹ Dr John Paulley wrote: 'I assessed that paper. It totally failed to recognize that ongoing life situations were more relevant than a single event, or to assess the meaning of an event to an individual.' Note on draft transcript, 13 October 2000. See Piper D W, McIntosh J H, Ariotti D E, Calogiuri J V, Brown R W, Shy C M. (1981) Life events and chronic duodenal ulcer: a case control study. *Gut* 22: 1011–1107.

²² See, for example, Ellard K, Bearepaire J, Jones M, Piper D, Tennant C. (1990) Acute and chronic stress in duodenal ulcer disease. *Gastroenterology* 99: 1628–1632.

Dr John Paulley: I was very glad to hear Richard Doll mention the foremen, because this was independently confirmed in a separate study in the USA.²³ It raises the question, when we are talking about psychosomatic disease, what do we really mean? The fact that this group of people who'd picked themselves out independently, did not mean necessarily that other 'work' that some people always thought was involved was also a cause. We went through the industrial revolution and the 'sweat shops' without any epidemic of peptic ulcer occurring.

I presented to the organizers of this meeting a short paper with references,²⁴ to support the fact that the rise since 1900 had been real and not imaginary; this was dependent on hard evidence, hard evidence of perforations, hard evidence by Stewart on consecutive autopsies,²⁵ and the rise continued until 1939. By 1945 the rise had begun to flatten out and by 1950 it had gone down substantially, except in Germany, where the fall didn't occur until 1965. I have always felt that that had something to do with the persistence of the turmoil of war in Germany, as opposed to this country, where it took less time to settle. What I want to point out particularly in relation to this conference is that the fall was being recorded *before* the H2 receptor antagonists were introduced, some 15 years before that, and 40 years before Warren and Marshall's discovery of *Helicobacter*.²⁶ I think that this is very critical to the question that we were asked to address, that is 'the rise and fall of peptic ulcer'. Clearly the H2 antagonists and the drugs against *Helicobacter* made an impact on this disorder, but were not available until several years after the 'fall' in incidence.

I read a paper as a medical student at the Middlesex Hospital Medical Society in 1938, just before the war, because ulcer was such a scourge. Many patients in the wards were found connected to bottles of blood or milk. And music hall comedians used to make a joke of, 'Don't worry or you will get an ulcer', so it was well known to be related to anxiety. I became interested in this. My paper at the Middlesex was called 'The neurogenic hypothesis for peptic ulcer' that went back to von Rokitsansky's discovery in 1841 of intracranial disease associated with upper intestinal ulceration.²⁷ That interest peaked with Harvey Cushing's Balfour lecture, 'Peptic Ulcer and the Inter-brain'²⁸ and, of course, this led to considerable research and interest in

²³ op. cit. note 20.

²⁴ A copy of Dr John Paulley's paper 'Peptic Ulcer: Rise and fall' was sent to the organizers of the meeting on 10 April 2000, together with a list of references. It will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

²⁵ Stewart M. (1941) *Text Book of Practice of Medicine*. London: Oxford University Press, 586–587.

²⁶ op. cit. note 231. Dr John Paulley wrote: 'Two studies should be mentioned, one by Lee Lander and Maclagan on gastric acidity in 100 medical students [Lee Lander F P, Maclagan N R. (1934) 100 histidine test meals in normal medical students. *Lancet* ii: 1210–1213] and the follow-up study 15 years later by Doll, Avery Jones and Maclagan [Doll R, Avery Jones F, Maclagan N F. (1949) Gastric secretion and subsequent dyspepsia. *Lancet* ii: 984–985].' Letter to Dr Daphne Christie, 9 April 2002.

²⁷ See von Rokitsansky C. (1849) *A Manual of Pathological Anatomy*. London: Printed for the Sydenham Society, 1849–1854, vol. 37.

²⁸ Cushing H. (1932) Peptic ulcer and the inter-brain. *Surgery, Gynecology and Obstetrics* 55: 1–34.

the connection between brain activity or emotions, and ulcer. My own feeling remains that the most important bit of that research was that which started with Beaumont's Alexis St Martin and his observations on fistula, and the subsequent more sophisticated psycho-physiological studies by Wolf and Wolff on 'Tom'.²⁹ I think it remains the most important basic research on peptic ulcer.

My own feelings about the reasons, or the possible reasons, for the rise are that there was very high unemployment following 1900, and the collapse of the shipbuilding and heavy industry, particularly in the north and west of Scotland. It was alleviated temporarily by the First World War, which required men and women to serve their country, only to be met by the disastrous aftermath following demobilization in 1919, when unemployment became so much more intensified. And then we had the general strike of 1926, followed by the Wall Street crash in 1929 and then the Jarrow marches. It was an intensive period of distress for people who had high expectations of 'a fit country for heroes to live in',³⁰ quite apart from the Education Act of 1918. So expectations had been raised, and then dashed, and the work on 'Tom' by Wolf and Wolff had shown just how much frustration and resentment played a part in exacerbating the activity of the gastric mucosa both in its motility and secretion.

The next big event in my opinion was the Beveridge Report, which offered security from the 'cradle to the grave' and was implemented in 1946.³¹ I personally feel that these events have to be taken very seriously as the reason for the rise and then the fall, or the beginning of the fall. The rest of the fall has been probably due to intervention with drugs, H₂ receptor antagonists and later *Helicobacter pylori*.

Booth: I wonder if I could just inject one factual point. One of the interesting statistics of that period, in the early part of this century, is the reason for a pension payment to individuals invalided out of the armed services. It is quite clear that following the First World War the major cause of people being invalided out was what was called 'disordered action of the heart', which Thomas Lewis worked on, was, in fact, an emotional reaction to the horrors of the trenches and quite reasonably so.³²

²⁹ Tom had a gastric fistula because of a sealed oesophagus therefore making it possible to assess the amount of acid secretion relating to his moods and emotional states. See Myer J, Beaumont W, Osler W. (1912) *Life and Letters of Dr William Beaumont: Including hitherto unpublished data concerning the case of Alexis St Martin*. St Louis: C V Mosby Company. Wolf S, Wolff H G. (1941) *Human Gastric Function*. New York: Oxford University Press. See also Wolf S. (1981) The psyche and the stomach. A historical vignette. *Gastroenterology* **80**: 605–614. Myers N A, Durham Smith E. (1997) A debt to Alexis: the Beaumont–St Martin story. *Australian and New Zealand Journal of Surgery* **67**: 534–539.

³⁰ Quotation from the British Liberal Prime Minister, David Lloyd George. from his Speech at Wolverhampton, 24 November 1918.

³¹ A report written by William Beveridge in 1942 that formed the basis for the social-reform legislation of the Labour government of 1945–50. See Great Britain. Committee on Social Insurance and Allied Services. (1942) *The Beveridge Report in Brief*. London: HMSO. Stewart J. (1943) The Beveridge Report in relation to the health services. *Transactions of the Royal Sanitary Association of Scotland*. Paper read at the 68th Annual Conference of the Royal Sanitary Association of Scotland, September 1943, 16–24.

³² See, for example, Illingworth C F W. (ed.) (1953) Incidence of ulcer, chapter VI, and The psychosomatic approach to peptic ulcer, chapter IX, in *Peptic Ulcer*. Edinburgh and London: E & S Livingstone Ltd, 69, 78–79, 115. op. cit. note 34, 97–109. See also Lawrence C. (1985) Moderns and ancients: the 'new cardiology' in Britain 1880–1930. *Medical History Supplement* **5**: 1–33.

Peptic ulcer wasn't a problem in terms of compensation payment, but in 1939–45, the major cause of invaliding out was, in fact, indigestion and peptic ulcer. Now to what extent is that because it had increased, or was it a change in professional attitudes? That is a question we ought to address.

Mr Raymond Kirk: I can't resist mentioning that my great chief Norman Tanner, looking at his 1000 haematemeses, did find a cause of stress during the war.³³ I remember he went through this for his Lettsomian Lecture and found an enormous peak; he went through all the papers to find out whether there was a big air-raid at that time or some disaster happened. The only thing he found was something in *The Times* that a new form of, I think, fruit fly had been discovered. We also know that during the Siege of Stalingrad the staff officers of the German army were a thousand miles back, living on the fat of the land, and the men at the front were digging up frozen turnips to chew. Amazingly there were very few peptic ulcers in the front, but the staff officers, obviously worrying about what awaited them from Hitler, were getting ulcers.³⁴

Pounder: I guess one of the problems is ascertainment: with the other ranks dying on the front in the trenches, nobody knew what they were dying from; whereas perhaps the officers were being diagnosed. Mike [Langman], you have used perforation rates in Britain as a surrogate marker for ulcer prevalence, in a system where there are hospitals, and you found a pretty firm end-point. What was the change in the prevalence of ulcers over the last 100 years?

Langman: Well it is clear, if you go back to 1860 when William Brinton wrote a book on gastric ulcer.³⁵ He did not mention duodenal ulcer and I think the reason for that is because it wasn't there. He would have found it, because this was all post-mortem statistics. In around 1890 a disease was described called duodenal ulcer, diagnosed almost for the first time.³⁶ It then rose in frequency, and between 1912 and 1924 (mortality statistics in the UK show it very well) there was an enormous increase in ulcer in older people, particularly gastric, but also duodenal, which eclipses it. Duodenal ulcer reaches a peak at about the end of the Second World War and then declines. How can one explain this? Firstly, although aspirin has been around for 100 years, it is very difficult to say that this could all be due to aspirin.³⁷ The two other dominant influences that one knows about are smoking and *H. pylori*,³⁸ which

³³ Tanner N C. (1954) Surgery of peptic ulcer. Lettsomian Lecture. *Transactions of the Medical Society of London*, 146–203, in particular page 199.

³⁴ Cleave T L. (1962) *Peptic Ulcer*. Bristol: John Wright and Son, 101.

³⁵ Brinton W. (1857) *On the Pathology, Symptoms, and Treatment of Ulcer of the Stomach: With an appendix of cases*. London: John Churchill.

³⁶ Saundby R. (1891) Clinical lecture on chronic ulcer of the stomach. *Lancet* i: 353–355.

³⁷ See, for example, Douthwaite A H, Lintott G A M. (1938) Gastroscopic observation of the effect of aspirin and certain other substances on the stomach. *Lancet* ii: 1222–1225.

³⁸ op. cit. notes 10 and 74.

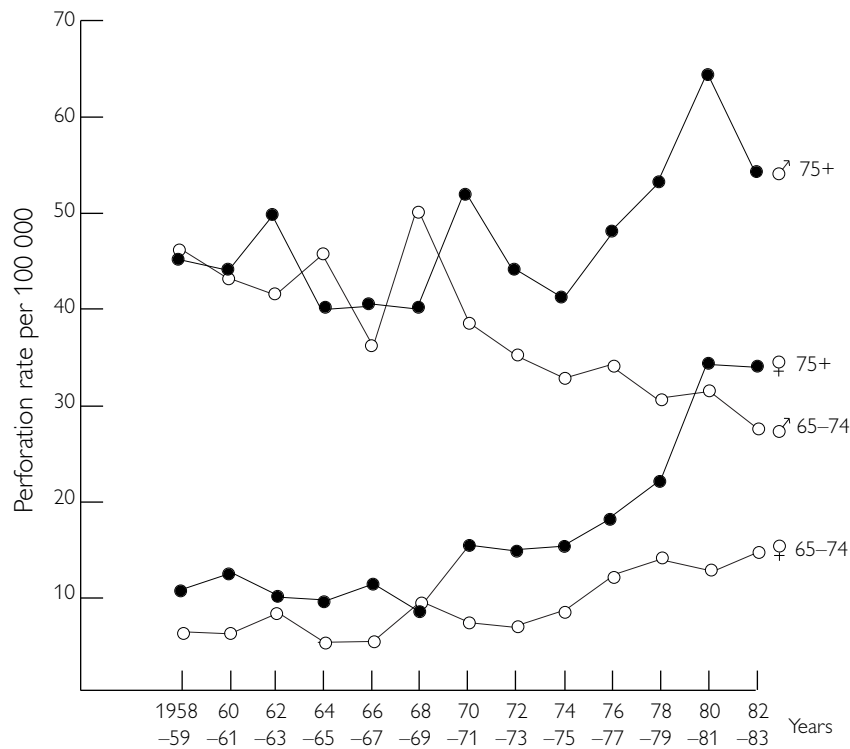


Figure 1. Age-specific duodenal ulcer perforation rates in England and Wales for men and women between 65 and 74 years, and 75 years and over. Figure redrawn from figure 2, *op. cit.* note 39. Permission granted to reproduce figure, Professor Michael Langman. © Professor Michael Langman, 2002.

interact. We know that the advent of cheap cigarettes came about during the First World War and so cigarettes became available to many people, and we also know that people who were unemployed preferred to spend their money on cigarettes and alcohol rather than on food. So it is quite likely this is how any gradient with unemployment and low social class is, in part, explained. What is not explained to my mind is why, if this is *H. pylori*-related disease, does the duodenal ulcer suddenly appear in the 1890s, when *H. pylori* was presumably around all the time. It is now beginning to fall, partly maybe in response to decreased smoking, but it doesn't seem to me that *H. pylori* being around all the time could explain it, unless there is something special about the way it has come and gone.

Pounder: And this is for the sake of completeness: in your graphs³⁹ you showed, in fact, a secondary rise of the perforation rate in the last couple of decades, particularly in the elderly (Figure 1). What happened?

Langman: I think that the main explanation of those graphs is that you have a cohort of people who have aged, who are particularly prone to ulcer. Now they are prone to ulcer because they have *H. pylori* infection, plus they smoke. They are also prone to it

³⁹ Walt R, Katschinski B, Logan R, Ashley J, Langman M J S. (1986) Rising frequency of ulcer perforation in elderly people in the United Kingdom. *Lancet* i: 488–492, page 490.

in response to any environmental influence, which will include anti-inflammatories, *Helicobacter* as described in Marshall's paper of 1985⁴⁰ and other causal factors.

Forrest: You may remember that Illingworth and Jamieson reported a survey of over 7000 cases of perforated peptic ulcer treated in Glasgow over a 20-year period.⁴¹ This included the war years of 1939–45 when there was an immediate increase in the incidence of perforation that peaked in 1940. A similar pattern was observed in London and other cities, which was believed to be due to the start of air-raids, but the peak in Glasgow preceded the Clydebank bombing raids. Thereafter the incidence of perforated ulcer steadily declined, for reasons that are still obscure.

Pounder: Professor Kenneth McColl from Glasgow, do you believe the 'shipbuilding hypothesis'? Glasgow still has so many peptic ulcers, even though shipping has declined.

Professor Kenneth McColl: Another factor, apart from *H. pylori* and smoking, that may have contributed to the change in the ulcer prevalence and also in the types of ulcer – particularly the shift from gastric ulcer to duodenal ulcer – may have been an improvement in the diet. *H. pylori* against a background of a diet short in antioxidants and high in salt will not produce duodenal ulcers, but it will tend to produce gastric ulcers, or gastric cancer. This is due to the fact that the combination of *H. pylori* infection, plus a diet low in antioxidants and high in salt, produces atrophic gastritis and hypochlorhydria. When the diet improved with imported fruit, and salt intake fell with refrigeration, then the gastric phenotype associated with the infection would change to a non-atrophic antral-predominant gastritis producing normal or high acid secretion. As a consequence the incidence of duodenal ulcer would increase and the incidence of gastric cancer would fall. More recently, the prevalence of *H. pylori* infection has fallen and consequently so has the incidence of duodenal ulcers.

Mr Roger Celestin: A very important paper that I think must be mentioned is the one in which Michael Atkinson was a co-author and this was work he did at the Hammersmith.⁴² He showed very clearly that a duodenal ulcer was a lifelong disease, due to a lifelong factor that first appeared in the second and third decades of life and became maximal in the fifth decade. In 1950 the average age of a male was 56 years. In 1850, it was 28 and, if we are going to look at the incidence of that disorder, we have got to take into account the age that people reached in the century before last, as a possible reason why so many ulcers were not seen between 1850 and 1900.

Dr George Misiewicz: Peptic ulcer is a socioeconomic disease. It's a sobering fact that it is now decreasing in incidence, quite independently of all that we can throw at it in

⁴⁰ Marshall B J, McGeachie D B, Rogers P A, Glancy R J. (1985) Pyloric *Campylobacter* infection and gastroduodenal disease. *Medical Journal of Australia* 142: 439–444.

⁴¹ Illingworth C F W, Scott L D W, Jamieson R A. (1944) Acute perforated ulcer. Frequency and incidence in the West of Scotland. *British Medical Journal* ii: 617–620, 655–658.

⁴² Atkinson M, Henley K S. (1955) Levels of intragastric and intraduodenal acidity. *Clinical Science* 14: 1–14.

the way of treatment. One can multiply the aetiological factors and one that hasn't been mentioned so far is housing. There is an association between overcrowding and gastric cancer.⁴³ Overcrowding equals *H. pylori*, equals peptic ulcer, or gastric cancer. Children sharing a bed, bad water supply and the like, all that has to be brought into the equation. The difficulty is to weigh these various factors in ulcer disease, and I don't know how to do that.

Mr Frank Tovey: I don't want to pre-empt what I have been asked to say later on but, in response to Professor McColl, I think one of the biggest changes in this century, which took place between 1890 and 1900 was the change from stone ground to roller mills for wheat, completely removing all the bran and germ, resulting in an increased consumption of highly refined white flour. It may be the increasing consumption of refined carbohydrates, as distinct from unrefined ones, that could be a big factor during this century.⁴⁴

Pounder: I was interested in Ken [McColl's] comments about salt intake. I am sure it is known, although I don't know the answer, about the amount of salt that people have had in their diet over the last 100 years. Certainly, I know that if you want to damage a rat's stomach, hypertonic saline is probably the most effective way of producing acute, diffuse mucosal damage.⁴⁵ That's using concentrations of salt that you get from eating, for example, salted fish in the diet. Do you know about salt in the British diet?

McColl: As far as I know, when refrigeration and ways of preserving food other than salting came in, the salt intake fell. I believe salt intake was falling in the 1940s, early 1950s.⁴⁶

Dr Peter Hunter: I would like to mention two facts and ask a question. The first is that acute stress ulcers were first described by Thomas Blizzard Curling of the London Hospital⁴⁷ in patients with burns, and I wonder whether this might have had some effect in moving opinion towards stress as a factor, although, of course, Curling ulcers are not chronic.

The second minor point of fact is that Harvey Cushing's 1931 Balfour Lecture in Toronto about the association of peptic ulcer with the mid-brain was, in fact, published.⁴⁸ My third point is a question. The Canadian endocrinologist, Hans Selye,

⁴³ Barker D J, Coggon D, Osmond C, Wickham C. (1990) Poor housing in childhood and high rates of stomach cancer in England and Wales. *British Journal of Cancer* 61: 575–578.

⁴⁴ See pages 23–25.

⁴⁵ Fraser A G, Debnam E S, Dhillon A P, Pounder R E. (1992) Gastric epithelial cell proliferation and histological damage after hypertonic sodium chloride: the effect of variation in the strain of rat. *International Journal of Experimental Pathology* 73: 241–250.

⁴⁶ The average daily intake is now around 8–15 grams – approximately half the consumption in the nineteenth century. See Kurlansky M. (2002) *Salt: A world history*. London: Jonathan Cape. See also op. cit. note 58.

⁴⁷ Fitts C T, Cathcart R S, Artz C P, Spicer S S. (1971) Acute gastrointestinal tract ulceration: Cushing's ulcer, steroid ulcer, Curling's ulcer and stress ulcer. *American Surgeon* 37: 218–213.

⁴⁸ op. cit. note 28.

exerted great influence on medical thinking in North America and elsewhere, when he described the general stress reaction from stimulation of the adrenal gland.⁴⁹ I wonder whether his influence had anything to do with the fact that stress was connected with these disease processes?

Dr Gerard Crean: With hindsight, it is possible for us to think of rise and fall, and the changes that were occurring, but I just want to reflect for a minute on the extraordinary efforts that we were making. The great excitements that we had in thinking in terms of – for example, hormones and ulcers, sex differences in ulcers, pregnancy in ulcer – and the extraordinary commitment of people like Ivy, who were determined to find something in urine that would cure ulcers and make them go away.⁵⁰ Then Selye's work in relation to corticosteroids in ulcer and the possibility that the endocrine system was involved.⁵¹ Although these things had a marginal significance, nevertheless all of us were playing about with these ideas and thinking about them; and the effect of parietal-cell mass, of making it bigger or smaller, the effect of gastrin on it and so on.

Pounder: Going back, Nelson Coghill, would you like to tell us a bit about your memories of what was happening 30 or 40 years ago?

Dr Nelson Coghill: I can go back even further than that anecdotally. In 1938 in the final viva for the Membership [of the Royal College of Physicians] – those of you who have suffered from that will remember the format, rather terrifying. Something happened that has been indelibly imprinted on my mind. One can learn from examinations. When a condition's aetiology is unknown and the treatment is relatively unspecific, as was so in peptic ulcer, there may have been a tendency to prescribe excessive rest and to curb patients' activities for want of anything better to offer. I was reminded of this by this question. The examiner asked what advice I would offer a man in his late 50s who wanted to go to a dinner, he had a gastric ulcer and, as I was about to reply, he held up his hand and said, 'You must not tell him he should not go'. And I thought this illustrated very well the negative attitude he thought I would fall into, when I didn't know what else to do. Many patients were admitted for bed rest in those days and subsequently. After I joined the staff at the West Middlesex Hospital in 1947 Avery [Sir Francis Avery Jones] sometimes phoned me to ask about our admission rates for peptic ulcer, and the treatments we used. I have no doubt that

⁴⁹ op. cit. note 51. Dr Peter Hunter added: 'As early as 1920 Sir Arthur Hurst described the effect of mental and physical fatigue on the appearance of symptoms of duodenal ulcer'. Telephone call to Dr Daphne Christie, 10 May 2002. See Hunt T. (ed.) (1969) *Selected Writings of Sir Arthur Hurst (1879–1944)*. London: British Society of Gastroenterology.

⁵⁰ op. cit. note 127.

⁵¹ See Selye H. (1956) *The Stress of Life*. New York: McGraw Hill. See also Szabo S. (1985) The creative and productive life of Hans Selye: a review of his major scientific discoveries. *Experientia* 41: 564–567. *idem* (1998) Hans Selye and the development of the stress concept: special reference to gastroduodenal ulcerogenesis. *Annals of the New York Academy of Sciences* 851: 19–27.

he asked other people too. Horace Joules, who was a physician and Medical Director at the Central Middlesex Hospital, was concerned, quite rightly, at the numbers of patients with peptic ulcers being admitted to the Central and the time they spent in hospital. So Avery wanted support. In fact, his practices and ours were similar, but nevertheless the cost in hospital resources was considerable. One might compare that with the treatment for patients with heart attacks in those days, who remained in hospital for weeks. Perhaps in this context we should remember Richard Asher's notable paper in 1947 on 'The dangers of going to bed'.⁵²

Baron: I want to make some epidemiological comments in relationship to history, because other speakers have said that duodenal ulcer, in particular, came to prominence in the 1890s, Moynihan putting it on the map.⁵³ This is not what actually happened. It's all complicated by the fact that duodenal ulcer was not then a registrable cause of death. You couldn't die of a duodenal ulcer or register it, so the statistics are not reliable. But we should go back, as Michael Langman said, to look at the great advance of Susser's cohort model idea, that one should look not at what was happening when the person got his ulcer, or when he died of his ulcer, but what happened when he was born, in his early years. This Susser did for the UK data that were limited to the twentieth century.⁵⁴ He produced the concept that the ulcer diathesis was a disease established in childhood of early urbanization, whether it was food or water, or overcrowding, or, as we now know, in relation to cross-infection with *H. pylori*. But I have, over the last four years, since I retired, tried to identify every published report of every patient in the USA and in the UK with a gastric or duodenal ulcer in the nineteenth century onwards. And with Amnon Sonnenberg's epidemiological help, there simply was an explosive growth from the beginning of the nineteenth century, with only an occasional patient in the sixteenth, seventeenth and eighteenth centuries. Mathematically, the British and the American lines show exactly the same patterns with gastric ulcer in men increasing about ten to 20 years after the increase in women with gastric ulcer, and then duodenal ulcer (mostly men) increasing about ten to 20 years after the rise in gastric ulcer. If you look at all the monographs, articles and books on peptic ulcer in Britain, France, Germany or USA, they also show similar increases in parallel. I have also looked at the archives of all the teaching hospitals in London and New York. Only there can you see the actual diagnoses of both admission and of death. Please remember that from about 1840 in London, because of Hodgkin, learning from Paris, and thus from Berlin and Vienna, that the most vital duty of a physician was to get a post mortem.⁵⁵ We are talking now about necropsy rates of 80–100 per cent throughout the major teaching hospitals in

⁵² Asher R. (1947) The dangers of going to bed. *British Medical Journal* ii: 967–968.

⁵³ See page 8.

⁵⁴ Susser M. (1961) Environmental factors and peptic ulcer. *Practitioner* 186: 302–311. See also page 7.

⁵⁵ Kass A M, Kass E H. (1988) A year in Paris, in *Perfecting the World: The life and times of Dr Thomas Hodgkin in 1798–1866*. Boston: Harcourt Brace Jovanovich, chapter V, 85–103.

London, throughout the nineteenth century, so the data are absolutely clear in relationship to this ulcer increase.⁵⁶

One other point about Moynihan. Yes, he made his point, and his point was absolutely valid, his gastroenterostomy would cure every duodenal ulcer, but of course the acid was merely shifted to the jejunum and patients got their recurrences as stomal ulcers. And although Moynihan got the credit for suggesting that hyperacidity was the cause of duodenal ulcer, he was to point out carefully that his data came entirely from Adams, a GP in Belfast, at the turn of the century.⁵⁷

The other reason why the 1890s were important was because it was only then, if you had a severe pain and developed acute peritonitis, that somebody would open your abdomen and sew up your duodenal ulcer or gastric ulcer. Before then you died, unoperated, of peritonitis.

McCull: I think one very important key to understanding the duodenal ulcer epidemiology and prevalence, is gastric cancer. We now know that the two are linked by being mutually exclusive. The conditions in the stomach that lead to duodenal ulcer protect against gastric cancer, and the conditions that lead to gastric cancer protect from duodenal ulcer. Consequently, I think we have to look at the changing prevalence of duodenal ulcer against a background of the changing prevalence of gastric cancer.

The other important point, of course, is that the mortality from gastric cancer will reflect what was happening in the stomach some 20 years or so earlier. The rise in incidence of duodenal ulcers was followed some 20 years later by a marked fall in the incidence of gastric cancer. This change in the incidence of both duodenal ulcer and gastric cancer may be explained by a fall in incidence of atrophic gastritis in *H. pylori*-infected subjects. This change in the histological pattern of gastritis induced by *H. pylori* is likely to be due to an environmental factor such as diet. A fall in salt intake and rise in antioxidants could explain this change in the histological response to the infection.⁵⁸

Dr David Tyrrell: I wanted to say something as a historical viewpoint of somebody who was training in medicine about this key time of 1950. I had been functioning as a house physician, registrar, in a good professorial medical unit, and I think that all of us felt that we knew quite enough about the problems of peptic ulcer to be able to cope. Yet listening to all these wise people looking back, and how many unanswered questions

⁵⁶ Baron J H, Sonnenberg A. (2002) Publications on peptic ulcer in Britain, France, Germany and the US. *European Journal of Gastroenterology and Hepatology* 14: 711–715. *idem* (2002) Hospital admissions for peptic ulcer and indigestion in London and New York in the 19th and early 20th centuries. *Gut* 50: 568–570. *idem* (2001) Period- and cohort-age contours of deaths from gastric and duodenal ulcer in New York 1804–1998. *American Journal of Gastroenterology* 96: 2887–2891.

⁵⁷ Baron J H. (1986) Duodenal ulcer, hyperacidity and J C Adams of Belfast. *Theoretical Surgery* 1: 113–114. Kennedy T L. (1987) Duodenal ulcer, hyperacidity and J C Adams. *Ulster Medical Journal* 56: 77–78.

⁵⁸ See, for example, Sonnenberg A. (1986) Dietary salt and gastric ulcer. *Gut* 27: 1138–1142. Rydning A, Berstad A. (1985) Dietary aspects of peptic ulcer disease. *Scandinavian Journal of Gastroenterology Supplement* 110: 29–33. See also op. cit. note 46.

there were! We thought about the patient who came in with a severe haematemesis – I had about one a week. We transfused them, if they perforated or something like that, or would not stop bleeding, we would pass them to the surgeons. If not, we would give them rest in bed and we would deal with their gastric acidity by diet and so we were on course to handle their problem. And it is only in retrospect, of course, that one realizes that we weren't really sorting the thing out in any fundamental way. Our therapeutic approach was mainly palliative. But the regimen was there, and it was taught to students and registrars, and we believed we knew the right answers. So all honour to the people who went on asking questions and were not satisfied with the current teaching.

Professor Stewart Goodwin: There is another factor that I think obviously will come up later, but the age at which *H. pylori* infection is acquired is vitally important in the pathology seen in the stomach. When *H. pylori* is acquired early in life there is a pangastritis and this leads to reduction usually in the amount of acid produced by the stomach. Therefore, I would suggest that the rise in civilization if you like, which occurred in the 1800s, when people were less crowded at the end of the century, these people probably got their *H. pylori* infection later in life. When you get your *H. pylori* infection later in life [From the floor: Can you qualify early and late?]. Yes. Early is up to the age of five. Late is in the teens and twenties, by the time your gastric acid cells have matured, and as Hugh Baron has showed, there is a minimum amount of acid required for the development of duodenal ulcer.⁵⁹ So in many countries today, in Chile for example, in half the population their gastric acid level is below that required to form a duodenal ulcer. And this occurs in China and in Africa, and in many other places. So I submit this as an extra factor. I quite agree with all the other factors stated so far, but if you get your *H. pylori* infection early in life, you are less likely to have a duodenal ulcer than if you get it later in life and you get it later in life when you have a higher economic state of your life.⁶⁰

Dr John Wood: I would just like to give a personal anecdote on the causation of my own bleeding duodenal ulcer. An event that three people in this room witnessed at a meeting we had in Switzerland. At some stage in the past I was infected by *H. pylori*, possibly spending two years at Guy's Hospital, swallowing tubes for J N Hunt, or maybe as a child, it is impossible for me to determine that. Essentially as a consequence of being stuck in a tunnel in the demilitarized zone between North and South Korea, I developed claustrophobia and was unable to get on to aircraft. As I fly two or three times a month, this caused me immense stress, and at the peak of my maximum stress, I was persuaded to get on a flight to Switzerland for a symposium that we were all attending, and at that stage I developed a bleeding duodenal ulcer. I was found to be *H. pylori* positive, and I am absolutely convinced from a sample size of $n=1$ that a combination of *H. pylori* and extreme stress can cause bleeding duodenal ulceration.

⁵⁹ See pages 5 and 6.

⁶⁰ Dr Joseph Blau wrote: '*Helicobacter* infection beginning in childhood and rising with age does not coincide with the age incidence of peptic ulcer. Is it possible that *Helicobacter* is not the cause but prevents ulcers healing?' Note to Dr Daphne Christie, 30 October 2000.

McCull: If I could just come back on Professor Goodwin. I hear his point about the time in life when you contract the infection affecting the outcome. It's a theory that a few of us have put forward, but I must say that there isn't really any strong evidence at the moment to support that.

Goodwin: I agree with Professor McCull. There are still lacunae in this, but we need to look at it in an epidemiological fashion. To go back to his original statements about gastric cancer and atrophy. These occur in populations where people get their *H. pylori* infection early in life, I think he would agree with that. Do we all get *H. pylori* infection? Well, yes, but some only as a short infection I think, as the last speaker said when he swallowed his tubes and so forth. I agree that in children there is far greater transmission of *H. pylori*.

Pounder: Hugh Baron has always been interested in gastric acid and gastric function. Hugh, tell us about gastric acid and peptic ulcer disease.

Baron: In the nineteenth century there were many hypotheses for the pathogenesis of peptic ulcer, including acid, infection, ischaemia and toxins. Although hyperacidity seemed a fruitful model because of the success of acid-diverting and lowering operations, infection became a favourite in the early decades of the twentieth century after ulcers were produced in animals by bacteria extracted from patients' ulcers. In a two-day meeting of the Section of Medicine of the Royal Society of Medicine in 1922, there was remarkable unanimity in accepting the theory of the infective origin of gastric ulcers.⁶¹ Indeed, the eminent surgeon Lester Dragstedt's first paper in 1917⁶² was on this topic; he was persuaded not to continue along this avenue, but to return to gastric acid, leading to his triumph of applied physiology, truncal vagotomy, in 1942.⁶³

Doll: We need to remember that the aetiology of duodenal and gastric ulcer is different.⁶⁴ What has been discussed this morning has been rather confusing in that it hasn't always been clear that most of what has been said has applied to duodenal ulcer and that gastric ulcer is quite a different disease.

Pounder: Well, that might start an argument! Who will speak? Ken McCull. Are duodenal ulcers and gastric ulcers the same or different?

⁶¹ Bennett T I. (1922). Gastric ulcer. *Middlesex Hospital Journal* 22: 189–192. Section of Medicine. (1922) Discussion on the diagnosis and treatment of gastric ulcer. *Proceedings of the Royal Society of Medicine* 15: 1–36. Moynihan B, Walton A J. (1922) The treatment of gastric ulcer. *Lancet* i: 267–271.

⁶² Dragstedt L R. (1917) Contributions to the physiology of the stomach. XXXVIII. Gastric juice in duodenal and gastric ulcers. *Journal of the American Medical Association* 68: 330–333.

⁶³ Dragstedt L R, Owens F M. (1943) Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proceedings of the Society for Experimental Biology and Medicine* 53: 152–154. Dragstedt L R. (1945) Vagotomy for gastro-duodenal ulcer. *Annals of Surgery* 122: 973–989. Woodward E R. (1987) The history of vagotomy. Founder's Lecture. *American Journal of Surgery* 153: 9–17.

⁶⁴ See, for example, Eisenberg M M, Woodward E R. (1967) Gastric ulcer – a different disease from duodenal ulcer. *Pacific Medicine and Surgery* 75: 86–91.

McCull: Excluding ones that are in the pre-pyloric region, gastric ulcers are an entirely different disease from duodenal ulcers. Both types of ulcers are due to *H. pylori* infection, but the response to the infection producing the ulcers is totally different. In the duodenal ulcer you have a non-atrophic antral-predominant body-sparing gastritis, and that produces a high-acid output which gives the duodenal ulcer. In gastric ulcer, the response to infection in the stomach is entirely different. There is an atrophic gastritis extending right up into the acid secreting part of the stomach, producing low-acid secretion. It's the same histological picture in gastric ulcer as you get in people with gastric cancer.

Pounder: So duodenal ulcers are acid or something drilling a hole, whereas gastric ulcers are the stomach falling apart. It's absolutely straightforward now!

Langman: It depends what you mean. The two things about which we know most at the moment are anti-inflammatories and *H. pylori*. The association with *H. pylori* is much the same for gastric and duodenal ulcer, at least though rather stronger for duodenal ulcer. That for anti-inflammatories is exactly the same for complications. So we cannot explain easily any greatly differing incidence of duodenal and gastric ulcer through disparate influences of these two factors.

Baron: As far as I am concerned, peptic ulcers are all gastric ulcers.⁶⁵ Obviously there are gastric ulcers in gastric mucosa in the stomach. The duodenal ulcer is an ulcer in gastric metaplastic mucosa in the duodenum, induced by gastric hypersecretion and invaded by *H. pylori*.⁶⁶

Booth: May I choose another question – both for gastric and for duodenal ulcers – one of the things we have always looked at is genetics. So far as the ulcer story is concerned, Liverpool School has related ulceration to different types of blood group.⁶⁷ I would like to ask the epidemiologists what the evidence was in those days for the genetic hypothesis and, in particular, whether anybody had done any effective identical twin studies of either gastric or duodenal ulcer?

Forrest: Before we get on to twins, can I note that Hugh Baron's comments are supported by the work of John Rhodes, who worked with Anthony James when I was in Cardiff, which demonstrated the consistent presence of gastric-type epithelial metaplasia in the duodenum in patients with acid hypersecretion and duodenal

⁶⁵ Baron J H. (1955) Peptic ulcers can now be cured without operation. *Annals of the Royal College of Surgeons of England* 77: 168–173.

⁶⁶ Wyatt J I, Rathbone B J, Dixon M F, Heatley R V. (1987) *Campylobacter pyloridis* and acid induced gastric metaplasia in the pathogenesis of duodenitis. *Journal of Clinical Pathology* 40: 841–848.

⁶⁷ See Aird I, Bentall H H, Mehigan J A, Fraser Roberts J A. (1954) The blood groups in relation to peptic ulceration and carcinoma of colon, rectum, breast and bronchus. *British Medical Journal* ii: 315–321. See also Mitra A. (1971) Relation of ABO blood groups to duodenal ulcer and bleeding. *Journal of the Indian Medical Association* 57: 447–449. Niv Y, Fraser G, Delpre G, Neeman A, Leiser A, Samra Z, Scapa E, Gilon E, Bar-Shany S. (1996) *Helicobacter pylori* infection and blood groups. *American Journal of Gastroenterology* 91: 101–104. op. cit. note 71.

ulcer.⁶⁸ It was analogous to the gastric epithelial metaplasia of the lower oesophagus in those with acid reflux and Barrett's ulcer.

Pounder: Sir Richard, has anybody done effective identical twin studies?

Doll: We did study the genetics of gastric and duodenal ulcer, and we found they inherited differently in families.⁶⁹ If you had gastric ulcer, you had a greater proportion of gastric ulcers in your families, and the same applied to duodenal ulcers, and they were dissociated genetically. But, of course, there are factors in common, I don't deny that for a moment, with the two types of ulcer, but there are also important differences between them. The striking one in the 1950s was the socioeconomic difference. The gastric ulcer was a disease essentially of the poorer section of the community and the duodenal ulcer being a disease of the professionals.⁷⁰

Pounder: Now we know about *H. pylori* there's a pretty easy explanation for the social difference in the poor. Where they are all living close together, there was a much higher prevalence of *H. pylori*. The rich were no longer carrying the bacterium.

Doll: But they were having many more duodenal ulcers than the poor were.

Langman: It's a simple sidelight on the blood group data. I think the late Ian Aird at the end of the 1940s knew that people in the North, if I have this right, were more likely to be blood group O than blood group A. He also knew that gastric cancer was, as he thought, more common in Scotland than in England, so he made the leap of imagination that there might be a link with blood groups. It turned out that there was a link but it was the other way round, it was with blood group A for gastric cancer. I think it was Cyril Clarke and Richard McConnell who then took an interest in blood groups and showed an association with group O and with non-secretion.⁷¹ The non-secretion association has, I think, never been explained adequately, even through links with *H. pylori*. Blood group probably related more to complications, and bleeding in particular. Because the controls used at that stage were blood donor volunteers and the cases were people who had been blood grouped – the latter were very likely to be people who had bled. When a blood group ulcer association was sought for uncomplicated ulcer, it was weak or non-existent.

⁶⁸ Rhodes J, Evans K T, Lawrie J H, Forrest A P M. (1968) Coarse mucosal folds in the duodenum. *Quarterly Journal of Medicine* 37: 151–169.

⁶⁹ See Doll R, Buch J. (1950) Hereditary factors in peptic ulcer. *Journal of Eugenics* 15: 135–146. See also Eberhard G. (1968) Peptic ulcer in twins. A study in personality, heredity, and environment. *Acta Psychiatrica Scandinavica Supplement* 205: 7–118. McConnell R B. (1971) Genetics and gastroenterology. *Gut* 12: 592–598. Jensen K G. (1972) *Peptic Ulcer, Genetic and Epidemiological Aspects based on Twin Studies*. Copenhagen: Ejnar Munksgaard Forlag.

⁷⁰ See, for example, Langman M J S. (1974) Epidemiology of peptic ulcer, in Bockus H L. (ed.) *Gastroenterology*, volume I. Philadelphia: W B Saunders, 611.

⁷¹ Clarke C A, Edwards J W, Haddock D R W, Howel Evans A W, McConnell R B, Sheppard P M. (1956) ABO blood groups and secretor character in duodenal ulcer. *British Medical Journal* ii: 725–731. op. cit. note 67.

Kirk: All surgeons will have seen people who had duodenal ulcers that got better and then later developed gastric ulcers. I have only in a single case seen somebody with four ulcer scars, and a duodenal ulcer scar, and then developing a proximal gastric ulcer. One sees really a pattern of change: they develop with a high acid and, as Hugh [Baron] says, gastric mucosa around a duodenal ulcer, and then later on when the acid secretions have disappeared and the gastritic change has gone farther up, developing just beyond the mucosal juncture, a gastric ulcer.

Professor Timothy Northfield: One point about publishing the discussion of this particular meeting is that some of the remarks, for instance on whether duodenal ulcer and gastric ulcer are different or not, will be interesting reading for the next Witness Seminar in 30 years' time.

Pounder: Well, that's why we are putting it down in writing now. Now is the time to come back to 'Worry, Hurry and Curry', the three causes of ulcer disease. Frank Tovey, tell us your view.

Tovey: May I take that opportunity now? You mentioned curry. As far as I can tell from all the available evidence, there is no connection with curry. I went to work in Mysore in India in 1951. My major surgical problem among men was that of duodenal ulcer. It became apparent over the next two or three years that all the cases I was getting were from the well-irrigated areas where there was rice growing, and virtually none from the dry areas where the principle food was a type of millet. This led to me collecting information over the next 30 years, both by visits and by correspondence, from all over India, West Africa, East Africa, South Africa, plus two visits to China, and a dietary pattern did emerge.⁷² One could almost predict that where the staple diet was polished rice, you would find a lot of duodenal ulcer. Where the diets were largely millet or unrefined wheat or certain pulses, one found very little duodenal ulcer. All this, of course, was before the H₂ antagonist days. Much of the information was gathered from hospital figures and from surgery of duodenal ulcer and its complications.

If I could just illustrate this. In Kumudini, a rice-eating area, north of Dacca in Bangladesh, they were having up to 70 duodenal ulcer patients a week, and operating on 30. In one morning's outpatient clinic I saw nine, and five had pyloric stenosis. Whereas at Ludhiana in the Punjab, an unrefined wheat-eating area, in a similar-sized hospital, we went over the records for five years and collected 90 cases only (Figure 2). This sort of information relates largely to rural areas. Once you get into urban communities, it's much more difficult and there is a much more mixed diet.

⁷² Tovey F I. (1972) Duodenal ulcer in Mysore. Characteristics and aetiological factors. *Tropical and Geographical Medicine* 24: 107–117. Tovey F I, Tunstall M. (1975) Duodenal ulcer in black populations in Africa south of the Sahara. *Gut* 16: 564–576. Tovey F I. (1979) Peptic ulcer in India and Bangladesh. *ibid.* 20: 329–347. *idem* (1992) Duodenal ulcer in China. *Journal of Gastroenterology and Hepatology* 7: 427–431. *idem* (1994) Diet and duodenal ulcer. *ibid.* 9: 177–185. Wong B C, Ching C K, Lam S K, Li Z L, Chen B W, Li Y N, Liu H J, Liu J B, Wang B E, Yuan S Z, Xu C P, Hou X H, Zhang A T, Zheng Z T. (1998) Differential north to south gastric cancer: duodenal ulcer gradient in China. China Ulcer Study Group. *ibid.* 13: 1050–1057.



Figure 2. Map of India showing areas of high duodenal ulcer prevalence corresponding to the rice-growing regions.
Figure provided by Mr Frank Tovey.

This led to more research when I came back to England in 1967. First we did some work based in Mysore and then with Charles Clark at University College Hospital using various animal models. Using pylorus-ligated rats we were able to show that if we fed them on a north Indian Punjabi diet of unrefined wheat, we got very few ulcers after pyloric ligation, whereas on a south Indian diet there were numerous ulcers. By supplementing the south Indian diet with various items from the north Indian diet, we reduced the number of ulcers. We then were able to identify certain foods that were protective: unrefined wheat, wheat bran, certain millets and certain pulses. Among the pulses, one of the most powerful, from the point of view of protection, was what was called Horse gram, *Dolichos biflorus*. The protective effect lay in its lipid fraction. We concentrated on that. We were able to show with several animal models that both the

phospholipids and the sterols that you can get from the lipid gave protection.⁷³ The lipid from wheat bran, a soya, and ragi (*Eleusine coracana*), a millet, was also protective. Polished rice, depending on how long it is stored, becomes more and more ulcerogenic, due to chemical changes and the development of ketoaldehydes.

We are going to talk about *Helicobacter pylori* this afternoon. In China and India, in the high- and low-incidence areas of duodenal ulcer there is no difference in the prevalence of *Helicobacter pylori*, so it looks as though there must be some additional factor. We think that it is probably this dietary factor that increases the duodenal mucosal resistance to acid and pepsin and ulceration. Lack of this primary factor may lead to ulceration, which can then become secondarily infected by *Helicobacter pylori*.

Sir James Black: I know nothing about aetiology of course, but listening to all the experts this morning there are two implicit assumptions. One is that this is a purely human disorder and I can assure you I have seen a huge indurating duodenal ulcer in a cow. Dogs get them, we don't know how often, because the nature of animal husbandry and veterinary practice means you eat or kill or incinerate your subjects.

The second point I want to make is there is an assumption all through this that the patient is passive. I can tell you from nineteenth-century textbooks of pharmacology and therapeutics that antacids were on the go heavily, in the form of sodium bicarbonate. So your patient with pain soon learns that sodium bicarbonate relieves the pain, the sodium bicarbonate then interferes with the regulation of gastrin inhibition, so we get hypergastrinaemia, up regulation of gastrin receptors, and increases the number of enterochromaffin-like cells. So they can induce admirably their own disease by reacting to it, so I don't think this passive patient you seem to be talking of exists.

Paulley: I want to thank the organizers for inviting me, but also to say that I am disappointed that the last three sessions of what we were asked to address, which was the rise and fall of peptic ulcer, are going to be devoted to issues and interests that really are not related to the rise and fall, because as I've pointed out the rise occurred before the drugs – that was, of course, presumably due to the factors we have been discussing. But there must have been some major determinant that changed and that would be something that I thought the conference ought to be talking about. The most likely one seems to be in the stomach, secretions, acidity, pepsinogens and so on. We are very much involved in multicausality, we haven't heard much about it. Multicausality has quite clearly come to the fore, but I just wanted to ask Professor Langman about his link with smoking. Because it seemed to me that if smoking is an important factor in encouraging *Helicobacter*, which it may be, it is odd that the

⁷³ Jayaraj A P, Tovey F I, Clark C G. (1980) Possible dietary protective factors in relation to the distribution of duodenal ulcer in India and Bangladesh. *Gut* 21: 1068–1076. Jayaraj A P, Tovey F I, Lewin M R, Clark C G. (2000) Duodenal ulcer prevalence: experimental evidence for the possible role of dietary lipids. *Journal of Gastroenterology and Hepatology* 15: 610–616. Jayaraj A P, Tovey F I, Clark C G, Hobsley M. (2001) Dietary factors in relation to the distribution of duodenal ulcer in India as assessed by studies in rats. *ibid.* 16: 501–515.

decrease in smoking didn't coincide with a decrease in duodenal ulcer. So it doesn't seem to me that the timing of the smoking factor in encouraging *Helicobacter* fits well with the rise and fall, and I would like to ask him if he could explain that.

Pounder: Professor Langman, how does smoking cause ulcers and does it fit with changes in the prevalence of ulcer disease?

Langman: I wondered whether you might like to ask Richard Doll with his long-term studies of British doctors, with his interest in smoking in peptic ulcer in the past, as to what he thought.

Doll: Well, there's no doubt about the association. It has been demonstrated in most Western developed countries and equally there's no doubt that stopping smoking heals the ulcer more quickly than if the person continues smoking.⁷⁴ It plays a part, but it is a minor part. But it has played a part I would have thought in the increase, as Michael [Langman] said, earlier this century, and it has contributed to the decrease also, because smoking has become a lot less prevalent in the last 30 years, so I don't see any conflict there. But it is only a minor secondary factor, and one of the many factors that Paulley was referring to in the multifactor aetiology of the disease.⁷⁵

Professor Michael Hobsley: I wonder if I could take up the question of acid secretion in its relation to ulcer, because it is related to the smoking that we have been hearing about. I was asked to talk about my experiences 50 years ago and I approach this from the point of view of being part of an academic surgical department of which I was by far the most junior member, 49 years ago, anyway. The situation then was very interesting, because the treatment of duodenal ulcer formed about 40 per cent of all the major operations that the department undertook. Partial gastrectomy was the most important operation in the training of an abdominal surgeon. Most patients came to us in the department of surgery, not from physicians, but from GPs. That indicates what the GPs thought about the medical treatment at that time. From various items of suggestive evidence we thought that the point-prevalence of duodenal ulcer was something like 10 per cent of the population at that time. The majority of university surgical departments specialized in upper abdominal surgery: vascular surgery was only just coming in, and, of course, transplant had not really taken off at that time. Research was mostly conducted on gastric juice secreted into artificial pouches in dogs and usually demonstrated by people speaking in a Scottish accent at the Surgical Research Society. On the other hand, there were some people who emphasized the problem of reliable collection from the human intact stomach, and of course another very popular field of research was the problems produced by the operation of partial gastrectomy, which was the standard treatment. Intellectually, it was accepted that duodenal ulcer was 'caused', whatever that means, by 'too much acid',

⁷⁴ Doll R, Avery Jones F, Pygott F. (1958) Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet* i: 657–662.

⁷⁵ For a review see Lam S K. (1994) Aetiological factors of peptic ulcer: perspectives of epidemiological observations this century. *Journal of Gastroenterology and Hepatology* 9: S93–S98.

whatever that means. Hugh Baron helped us here; he pointed out a very interesting thing in his work; he said that above a certain level of acid, you were bound to get an ulcer or virtually so, below a certain level of acid, you never got an ulcer, but in between there was a band in which some people got an ulcer and some didn't. So it was quite clear that acid was not the only factor and it was quite clear to some of us, not perhaps to everybody, that there had to be some other factor.

I spent about 20 years of my research life trying to define the contribution of acid to peptic ulcer disease, by refining the methods of measurement.⁷⁶ And there were two refining processes that were necessary. One was to sort out what was the actual secretion of the stomach, when you were able to separate from it, mathematically rather than physically, the contributions of swallowed saliva and reflux from the duodenum back into the stomach. We were able to do this and we were able to define a pure gastric secretion, allowing also for losses through the pylorus that were going on all the time while you were trying to suck them out. The other refining process that we had to take on board was that Hugh Baron with his height, for no reason other than his height, makes a vastly different amount of acid to myself or to somebody five feet tall. So we had to take the importance of stature into account. The best parameter of body stature happens to be the total body potassium, but for practical purposes height is the best one to tell you the amount of acid that is coming out of the stomach.⁷⁷ Using those techniques we looked at the relationship of acid to ulcer. And what we found was exactly what Hugh had found. Despite all our refinements, we found exactly the same as he did, that above a certain level, one was virtually certain to get an ulcer, below a certain level no ulcer, and in between there was some possibility of an ulcer. In addition, when we related, using statistical techniques, the amount of acid produced by patients of a certain height with duodenal ulcer to the amount produced by patients of the same height who did not have a duodenal ulcer, in other words normal controls, we found that the whole Gaussian curve was shifted to the right.⁷⁸ It was possible from that to calculate that the effect of acid could be summarized in this way: that for any given degree of acid there was a certain chance of having a duodenal ulcer, and that that chance increased as the gastric secretion increased. I am talking about the maximal gastric secretion, elicited by the maximum intravenous histamine test. As the maximal gastric secretion went down, the chance of having an ulcer decreased until below a certain level there was no chance of an ulcer whatsoever (Figures 3 and 4).⁷⁹

⁷⁶ Hobsley M, Silen W. (1969) Use of an inert marker (phenol red) to improve accuracy in gastric secretion studies. *Gut* 10: 787–795. Whitfield P F, Hobsley M. (1979) A standardized technique for the performance of accurate gastric secretion studies. *Agents & Actions* 9: 327–332.

⁷⁷ Hassan M A, Hobsley M. (1971) The accurate assessment of maximal gastric secretion in control subjects and patients with duodenal ulcer. *British Journal of Surgery* 58: 171–179.

⁷⁸ Hobsley M, Whitfield P F. (1987) The likelihood of disease in relation to the magnitude of a risk factor. The example of a duodenal ulcer. *Theoretical Surgery* 2: 106–109.

⁷⁹ Professor Michael Hobsley wrote: 'As stated baldly here the argument may be difficult to follow. For details see Hobsley M, Whitfield P F. (1987) op. cit. note 78; Figures 3 and 4 of that article summarize the relationship between risk of having an ulcer and maximal gastric secretion.' E-mail to Dr Daphne Christie, 28 November 2000. See Figures 3 and 4.

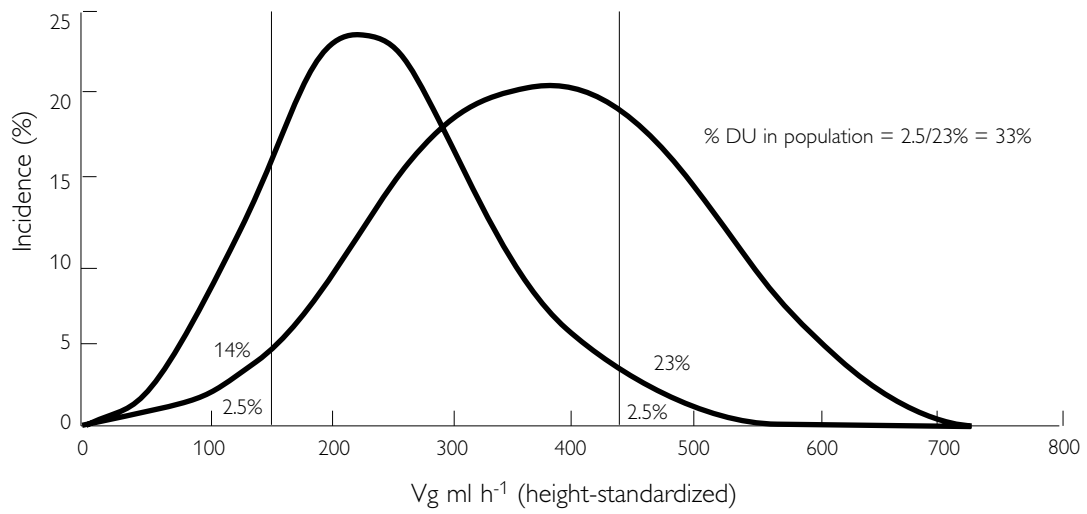


Figure 3. The distribution of maximal gastric secretion in control and duodenal ulcer (DU) subjects. Where V_g is the volume of gastric juice corrected for pyloric losses and duodenogastric reflux.

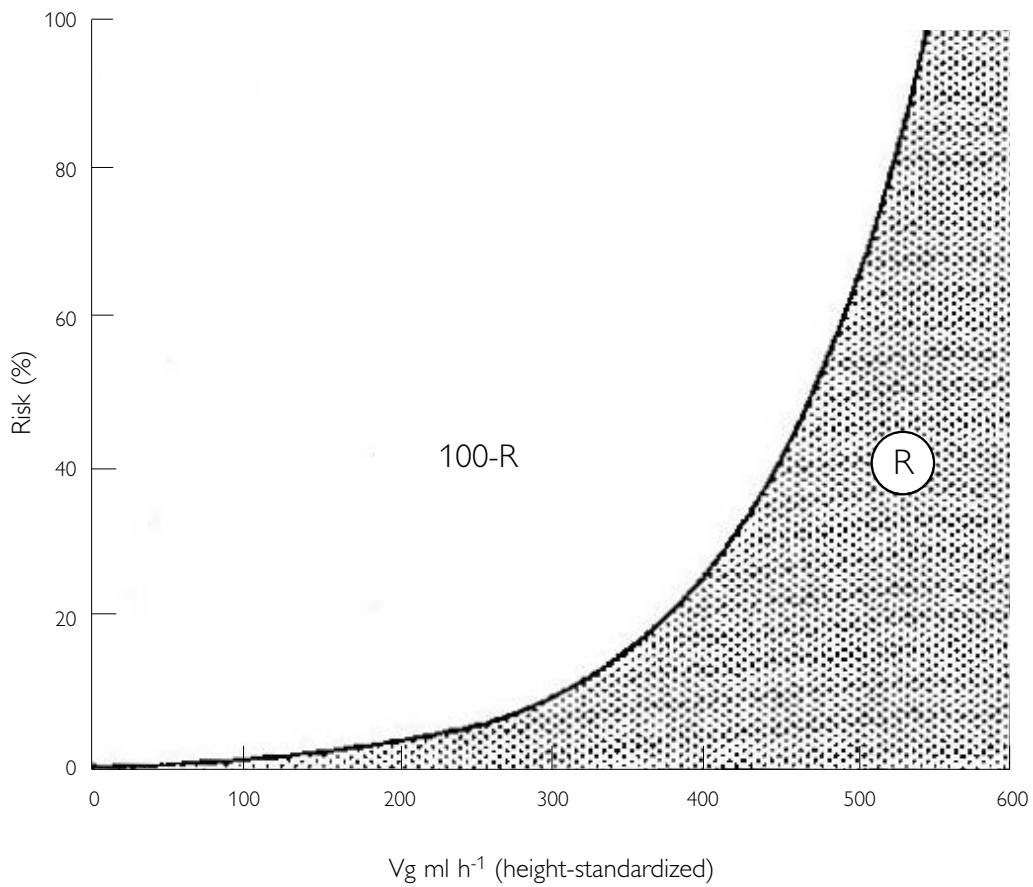


Figure 4. The risk curve of duodenal ulcer in relation to maximal gastric secretion. Where V_g is the volume of gastric juice corrected for pyloric losses and duodenogastric reflux. Figures 3 and 4 provided by Professor Michael Hobsley. © Professor Michael Hobsley, 2002.

This brings us to the association with smoking, because smoking is related to maximum gastric secretion of acid. This has been demonstrated by many centres, but I think we had excellent data on the subject.⁸⁰ Smoking puts up gastric secretion and it is possible to calculate that once you've taken the effect of smoking on maximal gastric secretion into account, then it has no further effect, no further connection, with the likelihood of a duodenal ulcer.⁸¹ So it is acting through acid.

Let me remind you of all the other facets about the link between acid and ulcer, that the acid is the final cause that punches the hole. People have talked about gastric ulcers being different from duodenal ulcers and, of course, they are – they are in the stomach, not in the duodenum. But Hugh is absolutely right and in cases of duodenal ulcer the gastric epithelium has grown down into the duodenum, just as in patients with oesophageal ulcer where the gastric epithelium has grown up into the oesophagus, just as in the ulcer that you get in the base of (not actually in) Meckel's diverticulum, that little diverticulum proximal to the ileocaecal valve. The ulceration producing bleeding in a baby is not in the diverticulum itself but in the ileum at the base of the diverticulum. All these things suggest that it is acid, getting to where it wasn't designed to be, that produces the ulcer.

Gastroenterostomy didn't just divert the acid from the stomach because, when you make a gastroenterostomy, surgeons know that if you do a barium meal you see barium in the bowel going back into the stomach – and you get a cycle of duodenal juices and gastric juices circling round there which have effectively reduced the gastric acid concentration in the stomach. Then again, what about the operations for duodenal ulcer? You removed the acid and the ulcer healed. Oh yes, there is a small recurrence rate, but very small indeed if the surgical vagotomy has been complete.⁸² Then how about vagotomy? Dragstedt introduced the operation because he thought that duodenal ulceration was due to increased basal secretion, and that vagotomy would reduce basal secretion. We have not found that. What we have found is that basal secretion remains the same after vagotomy.⁸³ It is true that basal secretion is higher in duodenal ulcer than in controls, but that is because maximal secretion is higher in duodenal ulcer than in controls, and basal secretion is a fixed proportion of maximal secretion, so of course duodenal ulcer patients tend to have a higher basal

⁸⁰ Whitfield P F, Hobsley M. (1985) Maximal gastric secretion in smokers and non-smokers with duodenal ulcer. *British Journal of Surgery* 72: 955–957. *idem* (1987) Comparison of maximal gastric secretion in smokers and non-smokers with and without duodenal cancer. *Gut* 28: 557–560.

⁸¹ Hobsley M, Whitfield P F. (1987) *op. cit.* note 78.

⁸² Maybury N K, Russell R C G, Faber R G, Hobsley M. (1977) A new interpretation of the insulin test validated and then compared with the Burge test. *British Journal of Surgery* 64: 673–676. Maybury N K, Faber R G, Hobsley M. (1977) Post-vagotomy insulin test: improved predictability of ulcer recurrence after corrections for height and collection of errors. *Gut* 18: 449–456. Butterfield D J, Whitfield P, Hobsley M. (1982) Changes in gastric secretion with time after vagotomy and the relationship to recurrent duodenal ulcer. *ibid.* 23: 1055–1059.

⁸³ Faber R G, Hobsley M. (1977) Basal gastric secretion: reproducibility and relationships with duodenal ulcer subjects, smokers and non-smokers. *Gut* 18: 57–63. Hobsley M. (1995) Dragstedt, gastric acid and duodenal ulcer. *Yale Journal of Biology and Medicine* 67: 173–180.

secretion.⁸⁴ But you don't reduce basal secretion by destroying the vagus. Vagal secretion remains identical and what you have done by vagotomy is you have reduced the *amount* of gastric secretion in response to histamine and to all other types of stimulant.

Pounder: One thing I know from measuring 24-hour intragastric acidity is that, if you have nothing in your stomach, your acidity will rise. So there's now the opportunity for you to dilute your acid with a cup of coffee. In the next session, we will be looking at some of the practical aspects of ulcer disease, particularly relating to diagnosis from the history, general practice, secretory tests, endoscopy and radiology. Finally, we will think about the role of surgery – the rise and fall of surgery relating to peptic ulcer disease.

⁸⁴ Roxburgh J C, Whitfield P, Hobsley M. (1994) Parietal cell sensitivity in humans: control and duodenal ulcer subjects, smokers and non-smokers. *European Journal of Gastroenterology and Hepatology* 6: 235–240.

SESSION 2: DIAGNOSIS

Crean: Because I was brought up, and most of us here were brought up, in the days before endoscopy was available, we had to make a diagnosis of duodenal ulcer based on symptoms, and decisions about surgery were based purely on symptoms. It has been said of duodenal ulcer that the cause of dyspepsia cannot be distinguished from symptoms alone, but we – and when I say we, I mean Wilfred Card, Knill-Jones and so on – set out to examine symptom–evidence in dyspepsia. We did a study lasting over 13 years, on over 1500 patients with dyspepsia. We devised a scoring system that was based on the simple notion of ‘weight of evidence’ that is common in Bayes’s theorem, which depends, of course, on sensitivity and specificity of symptoms.⁸⁵ Weight of evidence is a very crude measure of the evidence produced by symptoms, because it ignores the fact that many symptoms are dependent upon one another, it ignores the dependence of symptoms and in belly ache, for example, the dependence of symptoms turns out to be quite unexpected. If there is any pain it will be gastric pain, a pointing sign, but highly dependent on lots of other symptoms, symptoms such as hunger pain, pain relieved by food, antacids, after gastroscopy, and not surprisingly they are also highly dependent upon one another. But in the literature and in our textbooks, the symptoms of ulcer are described as pain relieved by food, by antacid, and so on. All of these things, although they are true, convey relatively little evidence in favour of peptic ulcer. I won’t bore you with the methods we use to calculate evidential scores but believe me, they are true and they do work.

I was going to tell you about some of the symptoms that were discovered in duodenal ulcer. Common symptoms include abdominal pain, gastric pain, epigastric pain, episodic symptoms. They are symptoms we speak of as indigenous that provide evidence for or against the diagnosis. So things like abdominal pain, epigastric pain are very common in ulcer. When present, they convey almost trivial evidence in favour of ulcer; when they are absent, however, they convey large amounts of evidence against. We think of them as ‘prescriptive symptoms’. When they are present, they prescribe the disease, they rule it into consideration. When absent, they rule it out. But indicants like food relief, antacid relief, have high scores in favour of ulcer being present, but the same amount of evidence against the ulcer when they are absent. So they are not really discriminative, we call them ‘descriptive symptoms’. Family history, episodes two to four weeks at a time, a pointing sign, a history for years, seasonal pain, hunger pain, pain mostly at night, but better still, pain that wakes a patient at night and is then relieved by antacid. Tagamet relief of course, previous X-ray, previous perforation, conveys a huge amount of information. If a guy comes in and says,

⁸⁵ Hirschfeld R M, Judge R D. (1969) Clinician vs computer: a study of the application of Bayes’s theorem to clinical diagnosis. *University of Michigan Medical Center Journal* 35: 32–35. Nicholls E M, Stark A E. (1971) Bayes’s theorem. *Medical Journal of Australia* 25: 1335–1339. See also Stigler S M. (1999) *Statistics on the Table: The history of statistical concepts and methods*. Cambridge, Massachusetts: Harvard University Press, 291–301.

‘Doctor, I have got belly ache and I have perforated and got these two years ago,’ what more evidence do you want? Although it contains huge amounts of evidence when present, it’s not the kind of question you ask a patient, ‘Excuse me, sir, have you ever perforated?’ It’s not the kind of question you ask, and this introduces me to the notion of expected evidence.

So what are the best symptoms, what are the best questions to ask in trying to diagnose a duodenal ulcer, what are the things we ought to be talking about, or teaching our students about? Well, let me tell you. In duodenal ulcer expected evidence in rank order: the question of a previous X-ray; does Tagamet relieve; do you have night pain; and do you take anything for it; the history: antacid relief, food relief, episodic pain, hunger pains, and so on. So, in fact, the data we have produced are quite hard data. The scores we have produced fit the standard quite tightly. So we think that symptom evidence instead of being soft measures are, in fact, perfectly hard measures and evidence can be manipulated numerically as well as any other measurable quantity.

Regarding the question of differential diagnosis between duodenal ulcer and gastric ulcer. Some of the textbooks give up and say you can’t distinguish, you have got to ‘scope and so on. But, in fact, with our database, looking at symptoms such as pain in the left hypochondrium, daily pain, no night pain, water brash, no heartburn, we were able to distinguish gastric ulcer from duodenal ulcer.⁸⁶

And you are going to ask me, how often does it work? Well, in fact, these scores can be taken and aggregated and you can calculate a probability of an answer of whatever the diagnosis might be. The calculation is if you got a probability greater than 0.9, which means pretty certain ulcer, that’s almost 90 per cent positive. In other words, if you reach a probability of 0.9 or something like that for duodenal ulcer, you are correct in something like 90 per cent of cases. And we can distinguish between gastric ulcer and duodenal ulcer with something like 80 per cent.

To summarize, there are all of us here who believe, at least some of us who believe, that you could distinguish cause of disability simply by listening to people. Nowadays, of course, if you fart you’re sigmoidoscoped and if you belch you’re endoscoped, nobody bothers to listen to you.

Pounder: You had a computer to work this out. What was its name?

Crean: GLADYS [Glasgow Diagnostic System for Dyspepsia]. We were taking symptoms as evidence, and it takes time and paying people like us takes money, whereas the computer costs very little really. The evidence can be elicited as well by computer as it is by you and me. But don’t tell the Government that. But the

⁸⁶ See, for example, Crean G P, Holden R J, Knill-Jones R P, Beattie A D, James W B, Marjoribanks F M, Spiegelhalter D J. (1994) A database on dyspepsia. *Gut* 35: 191–202. op. cit. note 88.

computer can elicit evidence just as well as we can and in some respects could be better.⁸⁷ [From the floor: They get viruses as well, Gerry.] Yes, of course.

Forrest: Gerry, you recently claimed, on the basis of your classical studies with Wilfred Card, that were a computer to be placed in every GP's surgery it would save 40 per cent of hospital admissions.⁸⁸ Did you ever prove it?

Crean: No.

Professor Colm Ó'Moráin: Gerry, as you said, symptoms were very important and very helpful in making a diagnosis, but quite often a chap who presents with a perforation, may be his first presentation with a perforation. And indeed the first presentation may also be with a major complication such as a haematemesis. And we know that some ulcers are present without any symptoms at all. How do you explain this spectrum?

Pounder: Can I put the question back to you, Colm? Can you tell me why people get ulcer pain? What's the cause of ulcer pain?

O'Morain: It's very difficult to explain, but the ulcer crater itself, I think, is just the tip of the iceberg. Of course, we know now there is much more associated with ulceration. So I think it is probably a reflection of more widespread inflammation releasing cytokines triggering afferent nerves that is causing the pain, rather than the tip of the iceberg, the ulcer crater, causing harm.

Pounder: Yes. I once wrote a review article on silent peptic ulceration.⁸⁹ I think there are two important facts. One is that, if you look at the literature, when people are admitted to hospital with a fatal bleed or perforation, only 50 per cent are aware they have an ulcer as they arrive in casualty. So a lot of the complicated ulcers appear to be asymptomatic. And it may be indeed that perforating ulcers, particularly acute perforations out of the blue, are not common or garden peptic ulceration. The second point, of course, is that many of these people are taking NSAIDs, which are anti-inflammatory, pain-relieving drugs. So they have got them causing the damage, as well as relieving the symptoms.⁹⁰

McCull: It's not just the complicated ulcers either, as you say, Roy, even the chronic ulcers are often asymptomatic. We recently endoscoped 100 *H. pylori*-infected healthy volunteers, and six of them had active duodenal ulcers, chronic ulcers. Only three of

⁸⁷ See Knill-Jones R P. (1985) A computer-assisted diagnostic system for dyspepsia (GLADYS). *Lecture Notes in Medical Informatics* 28: 215–226. Collins J S A, Knill-Jones R P, Sloan J M, Hamilton P W, Watt P C H, Crean G P, Love A H G. (1991) A comparison of symptoms between non-ulcer dyspepsia patients positive and negative for *Helicobacter pylori*. *Ulster Medical Journal* 60: 21–27.

⁸⁸ Card W I, Nicholson M, Crean G P, Watkinson G, Evans C R, Wilson J, Russell D. (1974) A comparison of doctor and computer interrogation of patients. *International Journal of Bio-Medical Computing* 5: 175–187.

⁸⁹ Pounder R. (1989) Silent peptic ulceration: deadly silence or golden silence? *Gastroenterology* 96: 626–631.

⁹⁰ Somerville K W, Faulkner G, Langman M J S. (1986) Non-steroid anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* i: 462–464.

them had had any symptoms whatsoever. So it may well be that half the chronic duodenal ulcers out there are totally asymptomatic. Why some get symptoms and how they get symptoms I don't think we have any idea. There was a paper years ago suggesting that the pain didn't come from the duodenum at all, but might be arising from the distal oesophagus.⁹¹

Pounder: Gerry, do you want to say a last word, otherwise we will move on?

Crean: Ken [McCull] has written about the cause of pain in duodenal ulcer and so on, in a paper with Fullerton.⁹² Then there are all these other people who have abdominal pains, functional dyspepsia, who have pain and no ulcer and no disease. In fact, we might postulate that today if you take the *H. pylori* out of the equation, and obviously that's very important, then the question becomes, 'Can you identify between ulcer disease and functional dyspepsia?' We think you can, by listening, without necessarily endoscopic.

Pounder: Well, non-ulcer dyspepsia is the disease of the future. Gerry, thank you very much.

Hunter: A question related to the general history of medicine. It is interesting that the scoring system for peptic ulcer symptoms based on weight of evidence and the scientific identification of the best symptoms and questions, just described by Dr Crean, was developed in Glasgow. For Glasgow is also the home of two other diagnostic scoring systems, the Wayne scales for diagnosing hyper- and hypothyroidism.⁹³ Is there any historical reason why all three scales came from Glasgow?

Pounder: The question is, 'Why do people in Glasgow always measure things?'

Crean: They are really quite independent. What I am talking about are the ideas generated by Wilfred Card who had got these before he came to Glasgow, so they are quite independent. In fact the systems were quite different anyway. The thyroid score system, I have forgotten the basis on which they made it, but it's quite different from Wilfred's ideas.

Dr Robert Logan: I would just like to pick up a point that Gerry Crean was making in talking about the Glasgow dyspepsia score and computerization.⁹⁴ You probably

⁹¹ Earlam R J. (1972) Further experience with epigastric pain reproduction test in duodenal ulceration. *British Medical Journal* ii: 683–685.

⁹² McCull K E, Fullerton G M. (1994) Duodenal ulcer pain – the role of acid and inflammation. *Gut* 35: 863–864.

⁹³ Dr David Tyrrell wrote: 'Professor E Wayne, Regius Professor of Medicine, is probably being implied – he did get interested in the symptomatic diagnosis of thyrotoxicosis.' Note on draft transcript, 8 April 2002. Dr Peter Hunter wrote: 'These scales combine both numerically weighted symptoms and numerically weighted physical signs, and are an invaluable aid to clear clinical thinking.' Fax to Dr Daphne Christie, 3 May 2002. See, for example, Billewicz W Z, Chapman R S, Crooks J, Day M E, Gossage J, Wayne E, Young J A. (1969) Statistical methods applied to the diagnosis of hypothyroidism. *Quarterly Journal of Medicine* 38: 255–266.

⁹⁴ See pages 31 and 32.

don't remember, I think probably about 12 years ago, a young research fellow ringing you up and asking you a question about this and how effective it was. Your response to me at the time was that the most useful box was a little box at the bottom of the front page, which was, 'What did the doctor think?'. However hard you tried to get the computerized system to work, there was something else above and beyond – which might have reflected the non-verbal aspects of the consultation or other cues that one might have got from interacting with the patient. There was something else that allowed you to say, 'No, this was more likely to be due to peptic ulcer disease or whatever' made an impression on me at the time and I haven't ever forgotten it.

Tyrrell: I have two points. One is a question. In doing this type of work, one usually looks to a gold standard diagnosis as the reference point from which you work out how effective your symptomatic diagnosis is, and I wondered what you used in your case? The other is an observation. We tried to make a diagnosis of upper respiratory disease and its different variants using symptomatic enquiries. It was very interesting that the disease patterns could not be distinguished by counting symptoms or frequency of symptoms that appeared in the checklist. But the doctor's view of the diagnosis was significant and correlated with virus isolations. I think this was because the doctors could sense which was the main area of the respiratory tract that was being involved by the virus and that was related to which virus was causing the infection. So sometimes just having the symptomatic list isn't adequate. Is that fair?

Crean: In our diagnosis we try to quantify uncertainty, since only God can be certain of anything.

Pounder: God and the endoscopists.

Crean: Well, the endoscopists have an error of 10 per cent anyway in one way or another. So every diagnostic statement, clinical and endoscopic or radiological was qualified by a probability statement to express the confidence limit that it was correct. The data that I am talking about are concerned with patients who were considered to have a certain diagnosis and so on.

Secondly, the bit about frequencies. Scores, it turns out, are independent of frequency. So that, although we teach that the symptoms are such and such, in terms of percentage frequency, in fact abdominal pain, the commonest symptom of peptic ulcer, is trivial evidence for the disease.

Finally to the bit about discrimination. Can I tell you a little story? This is early on in our business, we said 'Can doctors distinguish between duodenal ulcer and gastric ulcer?' and they said, 'Of course we can'. So four of us sat down together and we were given 70 cases of duodenal ulcer and 30 of gastric ulcer, and we were able to distinguish between them about 80 per cent of the time. Then we were asked to write down what are the symptoms that distinguish gastric ulcer from duodenal ulcer, we wrote down 23. We were asked the ratio of the differences in duodenal ulcer and gastric ulcer; of the 23 only six were, in fact, relevant, and of the 11 best symptoms

that discriminated we didn't even know about, we didn't recognize, like alcohol abuse, like duodenal ulcer being connected to it, and so on. In other words we were making the diagnosis discrimination, but we were over lucky, we were discrediting very powerful discriminant stuff which you and I also brought up, but don't recognize.

Pounder: That's called clinical experience, I think.

Baron: Dr Crean, of course, is dealing with words. English or Scottish is extremely rich in words to describe symptoms. But this is not so in all times and places. In my time in Malaya diagnosis was impossible, because there is only one word in the Malay language, 'sakit', which describes any symptom, you either have it there or you have it here, but the history is otherwise useless. I have been particularly interested in looking at all world literature back to about 2000 BC to describe what sort of symptoms people had. In other words did people really have ulcers in those days, which we know now from corpses that they did. Some of the descriptions are extremely clear with epigastric pain, spreading to the back at night. Similarly, you can pick out people who obviously had gastro-oesophageal reflux, which we thought was rare and is now more common than ulcers. You can also pick out in the eighteenth and early nineteenth century what they all talked about as 'dyspepsia'. They certainly didn't all have ulcers; they just had functional irritable guts. I found most interesting the philology, that a word for 'heartburn' is used in every single language, whether it is Slav or Chinese or Assyrian. Of course it isn't your heart that burns, but anatomically, as you know, the top of the stomach is called 'cardia' (heart), and patients and doctors were unable to distinguish between pain due to the heart and what was from the oesophagus. The actual symptoms of reflux are clearly described, so I have every reason to believe, irrespective of how many had ulcers, and whether ulcer frequency was as explosive as we believe it was from the early nineteenth century, that heartburn is *the* commonest condition of human alimentary suffering, but whether it was and is due to obesity or anything else, is beyond my knowledge.

Crean: There's one other bit about symptoms and that is what we mean about symptoms definition which is very important, and the error in eliciting symptoms. The error in eliciting as you know is huge, it is hardly worth asking. Flatulence, for example. We asked 40 distinguished doctors, like we have here, what they know of flatulence. Half of them said that it was because we loved to worry, another quarter said 'wind down the way', and ten or 15 said, 'Well, there's wind anyway,' and some of us said, 'Nothing whatever to do with it.' So we need to define symptoms like heartburn.

Pounder: Well, that's an important point. We will now move on, and introduce Roger Jones. He is going to talk about peptic ulcer disease and the role of general practice in the understanding of ulcer disease.

Professor Roger Jones: Thank you, Roy. I would first of all like to return briefly to the epidemiology. Dyspepsia is the cardinal symptom I suppose of peptic ulcer disease. It's a very common symptom, present in 30 or 40 per cent of the population if you

measure it over a one-year period. Yet only about a quarter of those people ever seek medical advice for that problem. The reasons for which they do so aren't intuitive. The reasons that people go to doctors with dyspepsia and other abdominal syndromes turn out to have much more to do with the construction that people place on their symptoms and the anxieties that they have about their possible significance, than more apparently likely reasons, such as the severity or frequency of pain. For example, when we studied a group of patients recently consulting GPs about dyspepsia, we found that about three-quarters of them were worried that they might have something wrong with their heart and about half of them were worried that they may have cancer. So it is, I think, quite important to look at the pattern and the determinants of healthcare-seeking behaviour when we come to the evaluation of people presenting in general practice and in secondary care with abdominal pain.

It's perhaps also worth reflecting in passing, as has already been mentioned, that a lot of these people, with and without symptoms in the general population, have probably got ulcers – and the focus that we have had in the meeting so far has been on ulcers as seen at post mortem, or under the surgeon's knife. We will be talking later about the endoscope, but I think it is also quite intriguing to think that a lot of ulcers come and go, symptomatically or not, without ever coming to the attention of any of us.

There are difficulties outside Glasgow of diagnosing patients with dyspeptic symptoms. I think it is a shame that the experiment of moving GLADYS into general practice or getting some sisters of GLADYS in other parts of the world into general practice and testing the ability to improve diagnostic accuracy in general practice hasn't ever really been tried. It does turn out that some of these diagnostic algorithmic systems, or Bayesian systems, are not very transportable geographically. They are rather culturally and geographically specific.

There are problems about making a clinical diagnosis in general practice. If you compare GPs' diagnoses with the endoscopic diagnosis made in open-access endoscopy services (and I set one of these up for GPs in a small cottage hospital in Hampshire about 20 years ago) there is usually a very considerable mismatch between the clinical diagnoses.

I went back to Osler, I thought this was the sort of thing I should bring to a meeting like this, to see if the same amount of diagnostic uncertainty pertained in the late nineteenth century. Of course it didn't. Osler was fairly clear about the symptoms of peptic ulcer; dyspepsia was clearly the most important one. Interestingly, writing in 1892, he described haemorrhage as being present in at least one half of all cases,⁹⁵ which is a very different experience from the one that we have now. He goes into a good deal of discussion about pain and the pattern of pain and indeed the posture of the patient in pain, interesting thought, to distinguish between gastric and duodenal ulcer. And we all know, of course, that the physical examination is very important in diagnosing peptic

⁹⁵ See Osler W. (1892) Section III. Diseases of the digestive system. 6. The peptic ulcer – gastric and duodenal. In *The Principles and Practice of Medicine*. Edinburgh, London: Young J Pentland, 368–376.

ulcer. I was rather alarmed to read his last paragraph, which said that, ‘Tenderness on pressure is a common symptom in ulcer and patients wear the waistband very low. There may be a painful point of very limited extent, most frequently an inch or two below the ensiform cartilage. In old ulcers with thickened bases an indurated mass can usually be felt in the neighbourhood of the pylorus. Pressure should be made with great care as rupture of an ulcer has been induced by careless manipulation.’ I’ll pass this on to my GP colleagues and we will have even less accurate ulcer diagnoses.

So the question really in general practice is how do you sort this out? About 10 per cent of the consultations that we have in general practice are to do with upper and lower digestive problems. Even if we take John Fry’s inflated figures from the 1970s relating to a list the size of 2500 patients,⁹⁶ we will only see less than a handful of new peptic ulcer patients each year. Most of the patients we see with ulcer-like dyspepsia don’t have ulcers. The questions really are to what extent is the clinical evaluation reliable? At what point should we start doing other investigations, what are the arguments for and against early endoscopy, what’s the role of testing for *Helicobacter pylori* in patients? Marshall Marinker made the important comment on the role of the GP in this regard. The role of the generalist is to marginalize danger, while the role of the specialist is to marginalize uncertainty. So the GP’s task is to try to pick up that minority of patients who are likely to have an ulcer, or cancer for that matter, and deal with them expeditiously, while using time as a diagnostic tool for the remainder. And it may or may not matter which particular algorithm we use to achieve that.

Northfield: You mentioned John Fry. My memory is that he particularly highlighted the difference between hospital practice and general practice. He had been a student at Guy’s Hospital where I was, and the population of ulcers that he had seen there had a very different prognosis, much more severe, went on causing trouble, and were very different to what he saw out in general practice, where he found that the average ulcer ‘burnt itself out’ within about seven years.

Jones: In typical cases symptoms tend to recur periodically for five to ten years. John Fry was a GP in south London who to the end of his life, with paper and pencil only, recorded meticulously the patients that he saw in his practice in Beckenham. This is an extract from a book called *Common Diseases*, published in 1974:⁹⁷ ‘In typical cases once begun, symptoms tend to recur periodically for five to ten years, and then to diminish in frequency and severity, finally ceasing as the person becomes older’. An interesting observation, I don’t know to what extent that is borne out by others’ observations. Of course John Fry’s observations were made on a singular population.

Hobsley: *A propos* flatulence, may I have a definition of dyspepsia please?

⁹⁶ See Fry J. (ed.) (1977) *Trends in General Practice*. London: British Medical Journal.

⁹⁷ Fry J. (1974) *Common Diseases*. Lancaster: MTP Press. See also See Reynolds L A, Tansey E M. (eds) (1998) *Research in General Practice. Wellcome Witnesses to Twentieth Century Medicine*. vol. 2. London: The Wellcome Trust, 80–83, 131.

Jones: I thought you were going to ask something else. It has moved on hasn't it? We started getting very clever about dyspepsia in the 1980s with working parties talking about reflux-like dyspepsias, epigastric ulcer-like, dysmotility-like, and I think Robin Knill-Jones collected about 23 different definitions of dyspepsia.⁹⁸ I suppose the definition that people work with now is 'upper abdominal or epigastric pain related to food and likely to be related to the gastrointestinal tract'. It's probably as broad as that. And I think it is true to say that the subclassifications of dyspepsia, with the exception of very typical reflux symptoms and very typical irritable bowel symptoms, have not helped us to target investigations or therapy.

Hobsley: May I just add a sort of supplementary comment to that? Earlier this morning, pain in the left hypochondrium has been mentioned.⁹⁹ Now a very eminent surgeon, Sir Gordon Gordon-Taylor, always claimed – I am not sure how true it was – that pain in the left hypochondrium was most often due to gall bladder disease.

Jones: Because the gall bladder is a midline structure embryologically and is then secondarily moved over to the right of the liver, but it's basically a midline structure and the pain can be midline, it can be on the right and it can be on the left.

Pounder: Let us now move to another way of diagnosing peptic ulceration – radiology.

Professor Robert Steiner: With the discovery of X-rays by Röntgen in 1895 it is not surprising that a worldwide effort started to visualize the gastrointestinal tract, and to establish normal and abnormal criteria for diagnostic purposes. However, it took quite a number of years to arrive at satisfactory answers and develop acceptable X-ray images, both from the patients' and clinicians' point of view. To begin with, the examinations were very unpleasant, terribly time consuming and the results not very convincing.¹⁰⁰

My own experience in radiology started in Sheffield in 1944, and then Hammersmith Hospital where I moved in 1950. From the patients' and radiologists' point of view the examinations were fairly straightforward, but one still had to dark-adapt for fluoroscopy about 15 to 20 minutes before the examination could start – rather frustrating! Fluoroscopy was primarily used as a localizing exercise for suspected lesions, often difficult to see on the fluorescent screen, many films had to be taken to confirm or exclude pathology. The films were processed in an old-fashioned dark room. In this wet state they were difficult to examine properly before the patient could leave the department. All this was very time consuming: 30–40 minutes per patient.

The problems changed very dramatically in the 1960s by significant technical advances. Firstly, film processing became automated, which produced dry films within

⁹⁸ Knill-Jones R P. (1985) A formal approach to symptoms in dyspepsia. *Clinical Gastroenterology* 14: 517–529.

⁹⁹ See page 32.

¹⁰⁰ An account of the history of diagnosis of peptic ulcer by Professor Robert Steiner was sent to Dr Daphne Christie, 4 October 2001 and 3 April 2002. This will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

minutes. Secondly, image intensifiers became available, which meant one no longer had to dark-adapt – a revolutionary step forward. Fluoroscopy could now be done in a fully lit room, the images became visible on a television screen through electronic manipulations. Patients too felt much happier with the proceedings, examination times were cut at least by half and all the hassle was taken out of the barium meal studies. There were many minor innovations in the following years, all leading to significant improvements in diagnostic accuracy. One rarely missed a peptic ulcer or carcinoma. At that time the barium meal was the examination of choice to visualize a peptic ulcer.

Now let me take a step further. With improvements in endoscopic techniques in the late 1970s, largely due to fibre optics and biopsy facilities, the big debate about which diagnostic technique was more accurate, reliable and cost effective came to a head. The answer soon became clear. Nowadays the barium meal is rarely used except for small bowel studies or when endoscopy is not available or is contraindicated.

The new imaging techniques such as CT [computerized tomography], MRI [magnetic resonance imaging] and ultrasound have little to offer in the diagnosis of the simple peptic ulcer, but can be useful if there are extra luminal complications such as malignant spread in carcinoma, fistulae, fluid accumulations or infections, particularly abdominal abscesses.

To conclude, the peptic ulcer that used to be the radiologist's diagnostic territory for nearly 80 years now belongs to the endoscopist.

Northfield: In my career, I had two interesting experiences of observing radiologists at work, during the period when radiology was in vogue. The first experience was with Richard Doll and Sir Francis Avery Jones at the Central Middlesex Hospital, London, where the radiologist Frank Pygott was remarkable in the clarity of barium meals and in his interpretation of these. He was able to identify ulcer craters in duodenal ulcers, as well as gastric ulcers. My second experience was at the Mayo Clinic, where two radiologists were able to carry out up to 100 barium meals in a morning, and to send the reported X-rays to a hospital two miles away by lunch time. They did this by using dedicated equipment and technicians, their contribution being to order extra views. The rapid delivery of the X-rays was by means of a tube system.

Langman: Whatever the possible virtues of radiology or endoscopy in diagnosis of ulcer, randomized trial by us showed no difference in outcome between diagnostic endoscopy and radiology. This caused outcry when presented to the British Society of Gastroenterology, although it actually meant that if better diagnosis (by endoscopy) did not influence outcome then treatment methods were inadequate.

Coghill: If I could just add a small historical anecdote to the diagnostic question. When I was in my second resident post in 1938, I had to look after the sick nursing staff, and there was a staff nurse with epigastric pain of some severity. She had two barium meal X-rays, performed by the senior radiologist at St Mary's who was also on the staff at this rather smaller hospital, the Hampstead General. He couldn't find

anything wrong. I asked Heneage Ogilvie to see her; he was one of the visiting surgeons. He consented to do a laparotomy and he found two gastric ulcers, one posterior, one anterior, both fixed. I suspect that the fixation of the ulcers had made it difficult for the radiologist to see them. He did a partial gastrectomy and she made a good recovery. A side thought on this case has bothered me. What do nursing staff feel about being allotted an unknown, young, different, inexperienced house physician to look after them every six months? The second case illustrates the difficulty of diagnosis, even with endoscopy. In 1947, shortly after I started at the West Middlesex Hospital, Marjorie Warren, the doyenne of geriatric medicine, asked me to see a woman of about 70 with a large posterior gastric ulcer seen on X-ray, diagnosis query carcinoma. At gastroscopy I was none the wiser. It wasn't possible of course to do a biopsy, with that instrument. She had a partial gastrectomy by John Ferguson, and made a good recovery. The ulcer was benign.

On the question of symptomatology, using the Australian biopsy tube¹⁰¹ which had its limitations, and which we modified, we tried to differentiate the symptomatology of people with gastric and duodenal ulcers, and others with non-ulcer dyspepsia. Without going into a lot of the details, we did find that the clinical differences, oddly enough, were sharper between peptic ulcers and non-ulcer dyspepsia, and in non-ulcer dyspepsia between patients with a normal mucosa and gastritis, than between gastric ulcer and duodenal ulcer. In most of the patients we did not find any evidence that gastritis caused symptoms. Felicity Edwards, who was working with us at the time, analysed patients with atrophic gastritis and found that an excessive number drank tea at a higher temperature than others would normally do. And she also found that there was a positive relationship with social class. The lower the class, the more likely they were to have atrophic gastritis.¹⁰²

Pounder: The advantage of bone china, I think. So Professor Steiner, thank you. I think we are now moving on towards endoscopy. John Lennard-Jones will introduce this topic.

Professor John Lennard-Jones: I think we should recognize the work of Schindler in the 1920s and then in the 1930s Hermon Taylor at the Royal London Hospital.¹⁰³

¹⁰¹ Dr Nelson Coghill wrote: 'We used the Australian gastric biopsy tube [Wood I J, Doig R K, Motteram R, Hughes A. (1949) A gastric biopsy: report on 55 biopsies using new flexible gastric biopsy tube. *Lancet* i: 18–21]. A small knuckle of mucosa was drawn through a hole by suction and amputated by a knife pulled up by the operator. We modified the instrument [Coghill N F, Williams A W. (1955) The technique of gastric biopsy. *Gastroenterology* 83: 60–70]. It had its limitations: the procedure was blind though it was possible to know approximately where in the stomach the biopsies were obtained. We used this instrument to study the causes of gastritis, and the symptomatology of patients with dyspepsia with and without gastritis.' Letter to Dr Daphne Christie, 2 April 2002.

¹⁰² Edwards F C, Edwards J H. (1956) Tea-drinking and gastritis. *Lancet* ii: 543–545. See also Edwards F C, Coghill N F. (1966) Aetiological factors in chronic atrophic gastritis. *British Medical Journal* ii: 1409–1415. *idem* (1968) Clinical manifestations in patients with chronic atrophic gastritis, gastric ulcer, and duodenal ulcer. *Quarterly Journal of Medicine* 37: 337–360.

¹⁰³ Taylor H. (1941) A new gastroscope with controllable flexibility. *Lancet* ii: 276–277. See also Davis A B. (1972) Rudolf Schindler's role in the development of gastroscopy. *Bulletin of the History of Medicine* 46: 150–170. Gordon M E, Kirsner J B. (1979) Rudolf Schindler, pioneer endoscopist. Glimpses of the man and his work. *Gastroenterology* 77: 354–361.

Schindler developed a semi-rigid gastroscope, but the endoscopist could not manipulate the end. Hermon Taylor developed a gastroscope, the end of which you could bend back in one plane. It was a side-viewing endoscope, you could bend the endoscope back so that you could see the lesser curve of the stomach and also the upper part of the posterior wall.¹⁰⁴ I vividly remember the endoscopic sessions at the Central Middlesex, because Sir Francis Avery Jones, of course, had learnt this technique from Hermon Taylor, who had started it at the Royal London. It was a pretty agonizing experience for the patient. I often used to have to hold the head, which was greatly extended. If they had prominent teeth, it made it difficult for the operator, and it was very difficult for the patient (see Figure 5).

I remember the excitement when Hirschowitz introduced the first model of a fibre-optic endoscope, which was in the early 1960s.¹⁰⁵ That was a side-viewing endoscope, and you could bend it back, but it had the great difficulty that it had a large element of torque so that when you twisted the proximal end you didn't know whether the distal end was moving in parallel with the proximal end. And then came the forward-viewing endoscope and I personally remember the excitement. This was the late 1960s, for the first time approaching the pylorus end on, passing through the pylorus and seeing for the first time a duodenal ulcer.¹⁰⁶

This afternoon we will be hearing about treatment trials. Sir Richard Doll's trials in gastric ulcer were done with barium meal in which he was able to measure the width of the ulcer and also the depth of the ulcer crater. I was interested in trials in duodenal ulcer. Although sometimes one can see the crater of duodenal ulcer on barium meal, not always, because of the scarring of the duodenal cap, and the ulcer, if visualized, was very difficult to measure. This difficulty in detecting and measuring the crater held back controlled therapeutic trials in duodenal ulcer until forward-looking endoscopy came in.

Pounder: I was Avery's last registrar at the Central Middlesex and was taught endoscopy by Avery. I remember how proudly we would write in the notes that we'd attempted to enter the duodenum. That was not quite as good as getting in, but at least we were proud to record that we had in fact seen the pylorus, if nothing else.

Dr Booth Danesh: In my first house job in surgery at Guy's Hospital in 1964, I was 'on call' six nights per week, receiving acute admissions one night in general surgery and the other in orthopaedic. I was suffering a great deal of epigastric pain, and barium meal diagnosed a high gastric ulcer. I was put on six weeks' bed rest, milk and

¹⁰⁴ Taylor H. (1941) op. cit. note 103.

¹⁰⁵ Hirschowitz B I. (1961) Endoscopic examination of the stomach and duodenal cap with the Fiberscope. *Lancet* *i*: 1074–1078. *idem* (1993) Development and application of endoscopy. *Gastroenterology* **104**: 337–342. *idem* (2000) Endoscopy – 40 years since fiber optics. Any light at the end of the tunnel? *Digestive Surgery* **17**: 115–117.

¹⁰⁶ Professor John Lennard-Jones wrote: 'By the nature of its design onward passage of a side-viewing instrument is performed blindly. The development of an end-viewing instrument allowed the circular aperture of the pylorus to be approached directly. On passing through it a duodenal ulcer was seen as a white area on the pink background of normal mucosa.' Note on draft transcript, 18 April 2002.

carbenoxolone (Pyrogastrone). On this regimen my pains persisted and repeat barium meal showed the ulcer was still there. I was condemned to have a gastrectomy, but I refused. It was recommended that I see the late Sir Francis Avery Jones. From my symptoms and barium films, he had some doubts about the diagnosis. He offered to endoscope me, highlighting its perforation risk. I do not know what type of endoscope he used, but I had the procedure done under general anaesthesia. When I came round, he told me, ‘Your stomach is better than mine’ and that I did not suffer from gastric ulcer disease, in fact, my pains were due to oesophageal spasm. Sir Francis suggested changing my job from surgery to medicine, and here I am today.

Pounder: You are still in remission? Very good. Now talking about endoscopies, Sir Christopher.

Booth: Well, I wondered whether I might inject a historical view on the history of endoscopy. It’s significant that the first pressure in this country for the provision of endoscopy services was a leading article in the *Lancet* in 1937,¹⁰⁷ which appeared in the same year as the foundation of the British Society of Gastroenterology and the same year, too, that its founder, Arthur Hurst, was made a Knight in the Coronation honours. So 1937 is an interesting time. That was the Schindler gastroscope. I would like to know from Lennard-Jones when the Hermon Taylor one came in. I can remember trying to use that and going to Avery Jones’s sessions at the Central Middlesex when I was first made a gastroenterologist. I confess that I never saw anything but inky blackness down this tube. I could never do endoscopy.

But I think we should pay a tribute to Hugh Gainsborough, a physician at St George’s Hospital, for the introduction of fibre optics. He happened to meet Harold Hopkins, who had already designed the zoom lens, and was a friend of my father’s who had done telephoto lenses. Gainsborough said to Hopkins, ‘Couldn’t we have something flexible, like a Ryle’s tube?’ Now this was in 1952 at a cocktail party, and it was following that that Harold Hopkins recruited Kapany to his department and together they published a paper in *Nature* in 1954 on the first fibre-optic bundle.¹⁰⁸

As Lennard-Jones pointed out, the only man who was interested in that in this country apart from one urological surgeon was Avery Jones, and Avery went to see Hopkins. It was he who persuaded Basil Hirschowitz at the Central Middlesex to get interested in the use of fibre optics. And the man to whom we owe the modern generation of fibre optics is Professor Takemoto of Yamaguchi University in Japan, because he was the man who first got hold of a Basil Hirschowitz instrument, made I think by GU Manufacturing in the USA. Takemoto produced the first fibre-optic bundle and a Japanese endoscope in Yamaguchi. Significantly, as Harold Hopkins told

¹⁰⁷ Leading article. (1937) Gastrosopy as an established method. *Lancet* ii: 1200–1201. See also Booth C. (1991) Clinical research in gastroenterology: history and future prospects. *Journal of Gastroenterology and Hepatology* 6: 161–165.

¹⁰⁸ Hopkins H H, Kapany N S. (1954) A flexible fibrescope, using static scanning. *Nature* 173: 39–41.

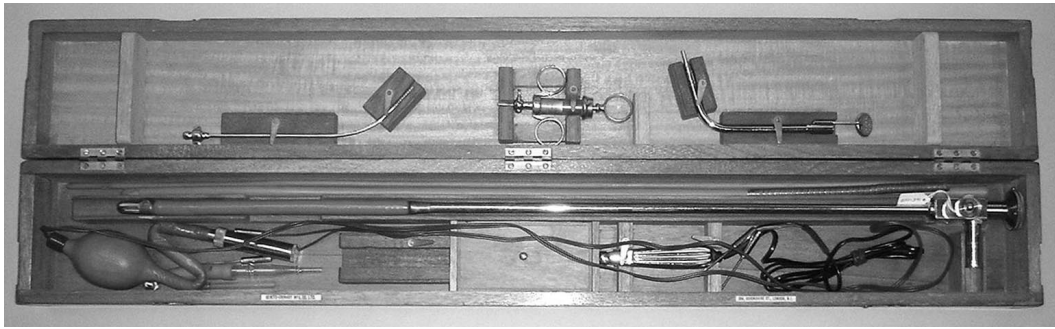


Figure 5a. The Hermon Taylor gastroscope. Photographs courtesy of Thackray Museum, Leeds.

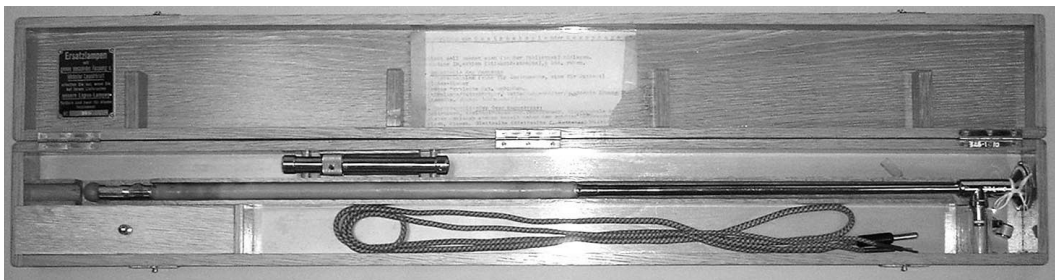


Figure 5b. The Wolf-Schindler gastroscope. Photographs courtesy of Thackray Museum, Leeds.

me, when they produced their first fibre-optic bundle in Japan they sent the original one to Harold Hopkins.¹⁰⁹

Pounder: Well, there you are, another example of something invented in Britain, developed in America, and manufactured in Japan. Other stories about endoscopy? I seem to remember that Jerry Kirk¹¹⁰ is a smuggler. Did you not smuggle an instrument into England?

Kirk: I did actually have a Hermon Taylor and a Schindler gastroscope. I was trained on the latter by Norman Tanner and I gave the Hermon Taylor one to an Indian friend who hadn't got anything. I think you [Pounder] have the Wolf-Schindler in your department at the Royal Free.

Pounder: That's right. But you imported it 'economically'?

Kirk: No, no. Absolutely honestly, as the day is long.

Pounder: Ah. As days have lengthened, he now denies it.

Crean: It was Wilfred Card who smuggled one in.¹¹¹

Lennard-Jones: You asked when Hermon Taylor started doing endoscopy. It was in the late 1930s. Avery Jones used to act as assistant to Harold Rodgers who introduced the Wolf-Schindler semi-rigid gastroscope at St Bartholomew's Hospital in 1934.¹¹² Later, Avery used the Hermon Taylor instrument when it became available. This is around 1938, 1939. Hermon Taylor, of course, is still alive and I think he developed the instrument in the late 1930s.¹¹³ You asked one other question. Avery's relationship with Hirschowitz. One of the fascinating things about that was, as far as I know, that Avery drew Hirschowitz's attention to the seminal paper by Hopkins and Kapany about the fibre-optic bundle.¹¹⁴ Avery read it in *Nature* and there are not many physicians who read *Nature*.

Pounder: Roger Celestin. Have you got any stories to tell us about endoscopy in its early days? As a man with a tube named after you, you must have!

¹⁰⁹ See Hopkins H H. (1980) The development of the modern endoscope. *NATNEWS* 17: 18–22. Linder T E, Simmen D, Stool S E. (1997) Revolutionary inventions in the 20th century. The history of endoscopy. *Archives of Otolaryngology, Head and Neck Surgery* 123: 1161–1163.

¹¹⁰ Mr Raymond Kirk wrote: 'My nickname "Jerry" was acquired at the end of the Second World War. After celebrating VE day in The Netherlands in the Royal Navy I was found in the position occupied by the chamber pot, under the bed – hence the name "Jerry".' Letter to Dr Daphne Christie, 25 April 2002.

¹¹¹ See page 46.

¹¹² Professor John Lennard-Jones wrote: 'Harold Rodgers, then a chief assistant at St Bartholomew's Hospital, London, went to Germany and brought back the instrument at his own expense. Avery Jones records that as a house physician he made himself available to hold the patient's head and "in no time, in early 1935, I was using it myself". Jones F A. (1986) Annual oration on peptic ulcer – in perspective. *Transactions of the Medical Society of London* 102: 101–112.' Note on draft transcript, 18 April 2002.

¹¹³ op. cit. note 103. Deceased 10 January 2001. See page 120.

¹¹⁴ op. cit. note 108.

Celestin: Thank you very much, Mr Chairman. Yes, if I can add on to what Professor Lennard-Jones said. In the middle 1960s quite a different flexible scope came into being. That was the gastrocamera with which you took, according to a certain protocol, 36 pictures at random, more or less. It was very much a hit and miss business. And we used it quite early in Bristol, but the results were far from gratifying. Then ACMI¹¹⁵ came out with one of the earliest of the side-viewing scopes, but there again the vision was very limited. We are now looking at 1966–67, and then suddenly the Japanese came out in 1969, 1970, with what were really reliable and superb instruments that changed the concept of clinical trials on peptic ulcer, because for the first time we could objectively see an ulcer decrease or increase in size with whatever form of treatment we were giving. In 1970 in Bristol we held the first national endoscopy meeting. Going back a couple of years, in 1968 I was doing an average of three operations a week for duodenal ulceration and I looked at the figures for 1966 that came from the Department of Health showing that about 27 000 vagotomies were done a year in this country, and that was an underestimate, obviously. And looking as far back as 1945 I worked out that between three-quarters and one million operations had been done by surgeons for peptic ulceration. In our results 80 per cent of the patients were reasonably happy, but 15–20 per cent really did not benefit that much from surgery. [From the floor: To put it mildly]. Yes, that's right. And 5 per cent were crippled by the surgery, and I certainly felt in 1968 as a surgeon that if I was going to have a 15–20 per cent failure rate, I could just as well be a barrister.

Then came the mood of looking at the parietal cell as a target for drugs at which time I had the great pleasure of visiting Sir James Black at Welwyn Garden City,¹¹⁶ when he introduced me to metiamide. By then endoscopy made all the difference and for the first time we had a method, a clinical method, that made trials with a new drug more objective and acceptable.

Dr Peter Down: Professor Pounder mentioned smuggling just now. I believe Harold Edwards smuggled an endoscope into this country in 1934. The cost of the Schindler gastroscope was £80 plus a £40 excise duty from Germany. This was quite beyond him as a mere private consultant surgeon starting his career at that time. But Hitler was just coming to power and he did the one good thing he ever did, according to Harold Edwards, he doubled the amount of [Deutsch] marks you could get per £1, which halved the price of the gastroscope. So all Harold Edwards had to do was to smuggle the endoscope into this country to avoid the excess duty. He did this by despoiling its brand new container box with the heel of his shoe to make it look old. But he had a

¹¹⁵ Mr Roger Celestin wrote: 'ACMI (American Cytoscope Makers, Inc) made the endoscope used at the time.' Letter to Dr Daphne Christie, 25 March 2002. For a report on the first commercially developed gastroscopes and their clinical use, see Hirschowitz B I. (1961) op. cit. note 105. Hirschowitz B I, Balint J A, Fulton W F. (1962) Gastroduodenal endoscopy with the fiberscope – an analysis of 500 examinations. *Surgical Clinics of North America* 42: 1081–1090.

¹¹⁶ The site of the Research and Development Division of Smith Kline & French Laboratories Ltd.

tough time with the customs man at 5.00 a.m. in Harwich I believe. He published a confession in the *British Medical Journal* 50 years later!¹¹⁷

Tyrrell: Just to add a point about Harold's [Hopkins] problems over getting the optical bundle principle into practice. He told me that, having done the initial work showing that the optical bundle would operate, you could get a good resolution picture at the end. He then tried to get one of the British optical manufacturers to produce something and develop it as an instrument. He failed. Then he went to the continent, including Siemens I believe, and failed again. That's just to fill a gap in the story. He didn't immediately want to have it done abroad, he wanted it to be built up as a product in this country.

Booth: I know that is in fact true, but I think the point that Lennard-Jones has made is a very important one. Avery Jones's position in this story is very important indeed. He was a remarkable man, he used to take his department up to Oxford, to the basic science departments, and go and listen to basic pharmacology and physiology, and things like that.

Tyrrell: I wasn't detracting from Avery Jones's important work, because the development work had to be done and initiated before there was anything for a clinician to work on.

Doll: I just wanted to remind us that the rigid gastroscope was a lethal instrument. We did do a survey¹¹⁸ and found that about one in 1000 gastroscopies with it had a fatal outcome. I perforated the oesophagus with it on several occasions, but fortunately all the patients recovered.

Dr Jean Guy: As a radiologist who didn't start radiology until 1968, I would like to provide a certain amount of corrective to this audience of endoscopists. I have done many thousands of barium meals since 1968, I am still performing barium meals, and still many diagnoses of gastric ulcer are being made and even more duodenal ulcers of course. I do think that the contribution of radiology in this meeting has been rather diminished.

Pounder: Not at all, we were sitting in admiration. There are clearly some people we can't endoscope. There are those who have advanced lung and cardiac respiratory disease and cardiovascular disease. There are also the lager louts. Lager louts are impossible as far as endoscopy is concerned, because they won't sit still. If you give them a sedative they get disinhibited, so they are ideal for radiologists [much laughter]. Now the last anecdote: Hugh, you used to do an endoscopy list on a Saturday morning at the Hammersmith didn't you?

Baron: No. I was brought up on the Hermon Taylor and Wolf-Schindler scopes and they were done on Saturday mornings at the Middlesex. Like Lennard-Jones, I found holding the head a dire responsibility, because if you let it drop, patients could easily perforate and die. But when in 1968 I was appointed to my first consultant post, at

¹¹⁷ Edwards H C. (1984) On the acquisition of a gastroscope. *British Medical Journal* ii: 1784–1785.

¹¹⁸ Jones F A, Doll R, Fletcher C, Rodgers K W. (1951) The risks of gastroscopy. *Lancet* i: 647–651.

the Prince of Wales Hospital, it was on condition that they bought me a fibre-optic gastroscope with a biopsy channel. It is all very well brilliant radiologists or brilliant endoscopists looking, but the science of gastrology began when one could biopsy anything and everything. I then had to take my gastroscope to the Hammersmith, where I had research sessions, because with my scope I could do biopsies, but the Hammersmith had only a Hirschowitz model, which could see but not bite.

Booth: If I could just answer the question about endoscopy at the Hammersmith. I think I am right in saying that a co-author on that study of the hazards of endoscopy was Charles Fletcher, who was a respiratory physician, and we know him so well from his work on smoking with yourself, Sir Richard. But the Saturday morning sessions were quite famous because Avery Jones used to come from the Central Middlesex to do the hollow organ gastroenterology at the Hammersmith when Sheila Sherlock was there studying the liver. Sheila Sherlock had an honorary appointment with Avery Jones at the Central Middlesex. She did the liver at the Central Middlesex and that's how it worked out.

Pounder: We are talking about the rise and fall of ulcer disease, and certainly at the Royal Free we peaked in terms of gastroscopy about five years ago. The numbers of endoscopies we are now doing are less and less, year on year, whereas everything else is rising – colonoscopies, ERCs [endoscopic retrograde cholangio-pancreatography], bronchoscopies. I am sure this is part of the peace dividend of eradicating *H. pylori*, having decisive treatment, and treatment being given rather liberally. Certainly, ordinary ulcer endoscopy is becoming less and less common as the years go by.

Now on to the role of gastrin. Graham Dockray is here from Liverpool, a city with a grand tradition in gastrin. Could you tell us about gastrin and peptic ulcer?

Professor Graham Dockray: Hugh Baron mentioned British physiology and the importance of gastric acid to it early on. Physiologists have always known that it is a pretty risky business having an organ that produces a 100 mM HCl, and it has never been a surprise that control of this system can go wrong and cause disease. I suppose about 50 years ago, it was clear that histamine stimulated acid secretion and while, I think, the people who were active in the field knew that gastrin probably existed, they didn't know much about its relative importance. In Liverpool, Rod Gregory thought the main thing to do was to find inhibitors of acid secretion. He was working on enterogastrone and urogastrone at that time, because he thought that they might prove to be clinically useful. He was using the best methods that he could to isolate enterogastrone and urogastrone and he knew that they were either proteins or peptides, but his methods really weren't good enough to purify them to homogeneity.¹¹⁹

Towards the end of the 1950s Rod Gregory had realized that when you were testing

¹¹⁹ Gregory R A. (1955) A new method for the preparation of urogastrone. *Journal of Physiology* 129: 528–546.

urogastrone or enterogastrone it was very important to establish a stable level of acid secretion and that the way that you did that was important. He had been doing this with histamine that wasn't, in fact, a very good way of doing it. Realizing this, I think he stumbled, in effect, into gastrin and that led him to ask whether it might be possible to establish a stable level of acid secretion with gastrin, simply for bioassay purposes. He and Hilda Tracy then tried to make some gastrin, and found that the available methods were just appalling. They knew they were appalling because they had got experience in protein and peptide chemistry from their work on urogastrone and enterogastrone. Ion-exchange chromatography resins had just become available, and they quite quickly made great improvements to the isolation of gastrin using these. As often happens in science, Gregory and Tracy then sent their first paper off to a journal and it was rejected with the comment that this work was absolutely irrelevant and nobody needed to purify gastrin. I think that may have been Hilda's first paper and she was so incensed by this that she said, 'We have got to use this method to isolate gastrin and show that there is some value to it'. Also, at exactly that time, Hilda had seen the first report of Zollinger–Ellison syndrome tumours,¹²⁰ which nobody has mentioned today yet, and she suggested to Gregory that these tumours might make gastrin and that would explain all the symptoms of these patients. They got their first tumour from Bill Sircus. Gregory was out of the lab when Hilda tested an extract on a conscious gastric-fistula dog and the acid just poured out. Gregory came back into the lab from his lecture, or committee, and found Hilda working hard to keep up with the acid that was coming out of the gastric fistula. They then realized that it really would be worthwhile to isolate gastrin from normal antrum and also from tumours of the Zollinger–Ellison syndrome, and that is what they set about doing. They did it very quickly, because they had the necessary track record in protein chemistry. My own opinion is that they wouldn't have got any further than that if they hadn't been able to form a really good collaboration with peptide chemists, who were in the chemistry department in Liverpool. It was quite unusual at that time because there were very few peptide chemists around. But one of the best, George Kenner, was in Liverpool and he said, 'There's no problem – we can do the sequence on this' and Gregory said, 'Gosh, you mean you determine the order of the amino acids?' and Kenner said, 'Yes, we will just do it'. And he did it. The first author on the sequence paper is also called Gregory, but it's a different Gregory. It's Harry Gregory, and the two are not related. It just happened that the graduate student who did the sequencing in Kenner's group was called Gregory.

In Kenner's lab at the time there was also a young peptide chemist from ICI who was on an attachment, and that was Jack Morley. Jack thought it should be possible to use the information somehow to make a drug. They then went into the study of structure–activity relations by mutating or changing each of the amino acids in gastrin, and looking at different lengths, until they found that the last, or C-terminal, four residues were all that were required for acid secretion, and they defined which

¹²⁰ Zollinger R M, Ellison E H. (1955) Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Annals of Surgery* 142: 709–728.

positions could be substituted with other amino acids.¹²¹ I think they were hoping to find a gastrin antagonist and they didn't succeed. They did, however, produce a compound that could be used for acid secretory tests. They knew that to patent it would not be possible if it was just the last four residues of gastrin. Gregory, and he always said afterwards he was just totally naïve, said, 'But you could put an unusual or unnatural amino acid on there and that would be patentable, for example you could put beta-alanine on, which we know stimulates acid secretion on its own, and isn't naturally occurring, and then it would be a drug and patentable'. So ICI went ahead and did that, and Gregory said afterwards, 'I never got anything for it'. So that's how pentagastrin came to have the structure that it has.

Recalling anecdotes about customs officers and importing material that we heard earlier.¹²² The definitive work, proving that all four forms of gastrin, large and small, sulphated and unsulphated, were present in Zollinger–Ellison tumours, was done on a massive tumour that had been resected in Los Angeles by Ed Passaro. Gregory had collaborated a lot with Mort Grossman in Los Angeles and Grossman said to Passaro, 'You have got to give this tumour to Gregory'. So then there was a question of how they were going to get this massive tumour to Liverpool. Grossman undertook to take it himself. They packed it in dry ice in a box that inevitably was very, very conspicuous. Grossman walked on to the plane with this and everybody showed a lot of curiosity at this box, and he said, 'Oh, it's just a tumour, you don't need to worry'. Then when he came to go through customs, the customs officer also saw that it was a very conspicuous package, and quite an unusual one, and asked him what it was. And having been forewarned by the reaction of his co-passengers, he played the same trick, he said, 'Well, it's a very, very big tumour and I don't think you want to look inside the box' and the customs officer said, 'OK'. And so that's how they got this 2kg tumour into Liverpool and proved definitively the structure of gastrin in gastrinoma. I saw their paper describing this work and that attracted me to the subject in the first place.¹²³ I wrote to Gregory and he offered me a job. It's the only job I have ever had, so I have always been very grateful to him.

Lennard-Jones: We were very excited in London when gastrin was discovered and realized that it was a circulating hormone. Therefore, it was very important that we try to measure it in blood. I spent some time in San Francisco, where we thought we might be able to develop a bioassay using the wall of a frog's stomach to separate two halves of a liquid-filled chamber. The stomach cells secrete acid in response to stimuli added to the solution in contact with the serosal surface. We tried setting this up at

¹²¹ See, for example, Morley J S, Tracy H J, Gregory R A. (1965) Structure–function relationships in the active C-terminal tetrapeptide sequence of gastrin. *Nature* 207: 1356–1359. Morley J S. (1968) Structure–function relationships in gastrin-like peptides. *Proceedings of the Royal Society, Series B*. 170: 97–111.

¹²² See page 46.

¹²³ Gregory R A, Tracy H J, Agarwal K L, Grossman M I. (1969) Aminoacid constitution of two gastrins isolated from Zollinger–Ellison tumour tissue. *Gut* 10: 603–608. See also Gregory R A, Tracy H J. (1975) The chemistry of the gastrins: some recent advances. *op. cit.* note 271, 13–24.

UCH with Duncan Colin-Jones. It didn't work. At that time we went to see Sir James Black, who was then working in Welwyn, and I remember going to his laboratory, which was testing potential H₂ blockers in a rat model. We saw that this technique was very appropriate for our problem and we set up a rat model for the bioassay of gastrin. We did detect a secretagogue using this technique and John Temperley, who was working with me at the time, did quite a lot of work with it. Then I became very excited during a visit to America to meet McGuigan who had just developed an immunoassay and this, of course, completely transformed the situation.¹²⁴ We brought the immunoassay back to London and we got it going at UCH, as I am sure others did also. McGuigan came to visit us to show us how to do it. That immunoassay was an enormous step forward.

Dockray: Just on that, through most of the 1960s Gregory devoted his time to making gastrin simply to give to other people, because he realized that he and Hilda couldn't do all the work themselves, and if the field was to progress he had to make gastrin for others. The first radioimmunoassay from Jim McGuigan's lab wouldn't have got going, and lots of other work wouldn't have been done, if Gregory hadn't been really quite selfless in this regard.

Kirk: I was so pleased to hear you mention Mort Grossman, because he must have contributed so much to British gastroenterology in training people in very good scientific methods. He used to come over to Liverpool quite frequently and I always remember saying, 'Isn't Liverpool a marvellous gutsy city?' and he said, 'Yes, it's very gutsy, but it's also very ugly. If God ever decides to give the world an enema, that's where he will put the nozzle'.

Dockray: I have heard him say things like that. I shared an office with him on his last sabbatical. I was very young and he was extremely senior and, I don't know why, but Gregory said, 'Mort, you can share an office with Graham'. For me it was a terrific year, and not wishing to pre-empt the discussion this afternoon on H₂ antagonists, we were sharing the office on the day that Jim Black's paper on H₂ antagonist came out in *Nature* in 1972.¹²⁵ I avidly read *Nature* as soon as it came out in the library, and I photocopied this paper immediately on one of these terrible photocopiers that we used to have in those days. So I had the photocopy of Jim's paper in my office and Grossman came in and said, 'What's this, what's this?' And he took the paper immediately before I could properly read it, and I think within a day had probably written and asked for some metiamide. All of their work over the next two or three years followed from that and I like to think that it would have been slower if I hadn't shown him that photocopy.

¹²⁴ McGuigan J E, Trudeau W L. (1968) Immunochemical measurement of elevated levels of gastrin in the serum of patients with pancreatic tumours of the Zollinger–Ellison variety. *New England Journal of Medicine* 278: 1208–1213.

¹²⁵ Black J W, Duncan W A M, Durant G J, Ganellin C R, Parsons E M. (1972) Definition and antagonism of histamine H₂-receptors. *Nature* 236: 385–390.

Pounder: In November 1976, on the very day that cimetidine was launched in the UK,¹²⁶ I was speaking in Liverpool, with Tracy and Gregory in the audience. I had terrible laryngitis, but I saw them looking with interest but concern – antigestrins hadn't won and an antihistamine was the winner that day.

Dockray: Well, there's still time.

Pounder: In this next session we are talking about the various treatments and trials associated with peptic ulcer. It's an enormous pleasure to invite Sir Richard Doll to start and tell us his view of things.

¹²⁶ See Pounder R E, Williams J G, Milton-Thompson G J, Misiewicz J J. (1975) Relief of duodenal ulcer symptoms by oral metiamide. *British Medical Journal* **ii**: 307–309. Blackwood W S, Maudgal D P, Pickard R G, Lawrence D, Northfield T C. (1976) Cimetidine in duodenal ulcer: controlled trial. *Lancet* **ii**: 174–176. See also Molinder H K. (1994) The development of cimetidine, 1964–1976: a human story. *Journal of Clinical Gastroenterology* **19**: 248–254.

SESSION 3: TREATMENTS AND TRIALS

Doll: As everyone here is well aware, 52 years ago when I started working with Avery Jones at the Central Middlesex Hospital, the treatment of gastric and duodenal ulcers was essentially the same. It was a bland diet and alkali for the relief of pain. Some people would just give alkali, apart from the relief of pain to neutralize the acid, and if the patient didn't get well on that, then bed rest, and if that was inadequate and it recurred sufficiently often, then surgery, and that was that. Most physicians had their favourite ancillary treatment that was added to it, phenobarbitone was particularly common and we gave phenobarbitone pretty consistently in the treatment of peptic ulcer at the Central Middlesex when we began in 1948. But even then doubts were being expressed as to whether the bland diet was necessary. I may say that as a student it was one of the things that made me interested in social medicine, the cavalier way in which the consultant would discharge a labourer from the ward of a teaching hospital and say, 'Well, now you have just got to go on fish and eggs and milk' and the poor man had not got a possibility of buying fish, which was relatively expensive, and certainly not living on a diet like that, it would have been utterly impossible, but that wasn't thought of. But doubts were being stressed as to whether this bland diet was of any importance. Ivy's textbook in 1950¹²⁷ said that there was really no evidence that a strict diet was any better than quite a mild regimen, and Morton Gill, I don't know whether he is still alive, but in 1947 he published a paper in the *Lancet* saying that he had treated 20 consecutive patients by hypodermic injections of distilled water and they had done just as well as a control series.¹²⁸ He didn't describe what the control series was, but judging by the way physicians, and surgeons for that matter, judged their therapy, it would have been by comparison with a series of patients they had had in the past, or with a series of patients that somebody else had reported on. As a result there were, of course, many, many treatments, some of them quite bizarre, that were published (Figures 6 and 7). I had a table at one time showing a treatment for peptic ulcer, beginning with each letter of the alphabet. Unfortunately I lost that table, or I would have circulated it now, but there was no difficulty in preparing it.

Clearly this was an unsatisfactory situation, and Avery and I, with the assistance of Pygott, the radiologist, set out to test a variety of these therapies one after the other. Of course, I had the added advantage of working with Sir Austin Bradford Hill and he had just published the results of the first trial of streptomycin for treatment of pulmonary tuberculosis with randomization of patients.¹²⁹ So it came quite naturally

¹²⁷ Ivy A C, Grossman M I, Bachrach W H. (1950) *Peptic Ulcer*. London: J & A Churchill, 1059.

¹²⁸ Gill A M. (1947) Pain and the healing of peptic ulcers. *Lancet* i: 291. Dr John Paulley wrote: 'This was to support his belief that claims then being made that histidine injections could heal ulcers were unjustified and were due to what is now called "placebo effect", and supports the need for research workers to try harder to exclude placebo effects.' Letter to Dr Tilli Tansey, 13 October 2000. See also Bulmer E. (1934) The histidine treatment of peptic ulcer. *Lancet* ii: 1276–1278. Wingfield A. (1936) Histidine treatment of peptic ulcer. *Postgraduate Medical Journal* i: 1156–1158. op. cit. note 155.

¹²⁹ See Hill A B. (1990) Memories of the British streptomycin trial in tuberculosis. *Controlled Clinical Trials* 11: 77–79.

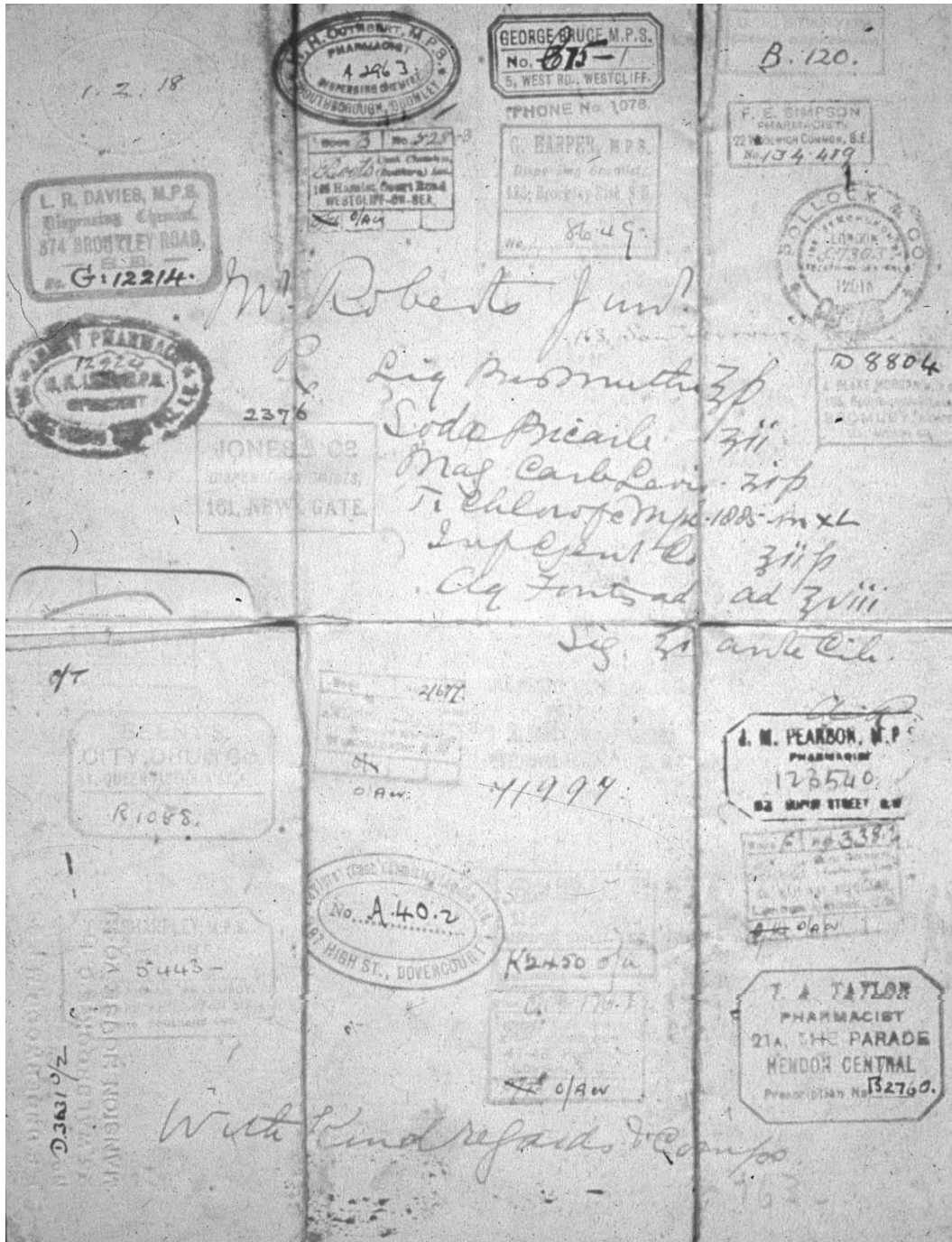


Figure 6. A prescription written for a duodenal ulcer patient in London in 1912. His son (who also suffered from peptic ulceration) said that his father always got a new bottle of the mixture whenever his symptoms recurred. It contained antacids, bismuth and morphine – hence the multiple pharmacy stamps whenever a new bottle was dispensed. Duodenal ulceration was a chronic disease. Photograph provided by Professor Roy Pounder.

to randomize patients in our trials. The idea of having concurrent controls, of course, had been accepted by, I think, most academics at that time, but most reports of physicians' favourite treatment were just their personal theories, not even having alternate patients and controls, in a concurrent series of controls. But we, of course, decided to do our trials with random allocation. We had so many therapies to test that we wanted to test three at once, and we did this by a means of a factorial design. In each block of eight patients, we would have the eight different possible combinations of the three treatments. The first trial was bed rest against outpatient treatment, phenobarbitone against placebo, and ascorbic acid against placebo. They were three treatments that could perfectly well be taken together as they were thought to act in different ways and combinations of two or three would not interfere with the effects of any of them. Over the next 20 years we tested 20 different treatments. There was one treatment that we didn't test and if we had we might have learnt something of considerable importance in relation to subsequent discoveries about *Helicobacter* – that was a treatment called Denol. But the manufacturers of this particular therapy were so aggressive that Avery and I, although we were perfectly willing to test patent medicines, were not prepared to cooperate with them. Denol had bismuth in it. Probably it would have been shown to be beneficial and might have led us into asking why bismuth was more effective than other alkali preparations.¹³⁰

One relatively patent medicine that we did try was an extract of liquorice. Liquorice was used by a pharmacist in Holland, who had a very successful practice, prescribing it for patients with peptic ulcers. So we tested carbenoxolone prepared from liquorice at the request of a small pharmaceutical company, and it proved to be really the only specific treatment for peptic ulcer before the days when we had the H₂ antagonists and began really to know something about the disease.¹³¹

But in the course of this series of trials we did show that bed rest did heal the ulcer, although it's not a very acceptable treatment to send people to bed for four weeks, but it did obtain a better result than letting people carry on with their work as outpatients.

The only other thing that was any good was stopping smoking, and we were able to demonstrate in a controlled study that it speeded up healing.

We were able to show, which was I thought most important, that the bland diet was quite unnecessary. Patients did just as well if they had meat and vegetables of all sorts. The only difficulty was in persuading people to have a normal diet, we felt that we had to advise them to avoid something and we did advise them to avoid fried food, just for the sake really of telling them that they were having some special dietary

¹³⁰ op. cit. note 218. See also page 81.

¹³¹ Carbenoxolone is synthesized from glycyrrhizinic acid, an extract from liquorice root. See Craig O, Hunt T, Kimerling J J, Parke D V. (1967) Carbenoxolone in the treatment of duodenal ulcer. *Practitioner* 199: 109–111. Langman M J. (1968) Carbenoxolone sodium. *Gut* 9: 5–6. Pinder R M, Brogden R N, Sawyer P R, Speight T M, Spencer R, Avery G S. (1976) Carbenoxolone: a review of its pharmacological properties and therapeutic efficacy in peptic ulcer disease. *Drugs* 11: 245–307. op. cit. note 215.



Figure 7. Until 1976, antacids were the only 'active' medical treatment for peptic ulcer – and there was a lot of competition for this market. Photograph provided by Professor Roy Pounder.

advice, but otherwise they had the normal hospital meals and they did just as well. Patients given milk drips did absolutely no better than patients not given milk drips. I have often recalled subsequently that I certainly never obtained a patient's specific consent for treatment of an ordinary diet versus a bland diet, and I have often wondered whether it in fact would have been possible to obtain in those days. People were so obsessed with the idea that a bland diet was essential for the treatment of peptic ulcer, that to tell a patient that they should stay in the hospital and have a normal diet, would have rather upset them. I don't think they would have volunteered to do it, because as I say it was so ingrained into people that they had to have a bland diet, but I have often thought that perhaps that was my most important contribution to gastroenterology, and certainly to public welfare: namely that it was quite unnecessary to have a bland diet if you had a peptic ulcer.

Guy: Was there such a thing as the milk–alkali syndrome, as the result of large doses of antacids and milk?

Pounder: It was before my time, but I think it was more an American problem. It was partly because American milk is fortified with vitamin D, so that if Americans drank a lot of milk, they were getting not only the alkali and calcium, but also they were getting the vitamin D that would induce hypercalcaemia.

One of the questions I was thinking about was informed consent, and how complicated this makes our lives now with clinical trials. I was also attracted by the factorial design – the opportunity to test three things simultaneously tends to be denied us these days. Everything is now done very carefully, one at a time.

Booth: It's not denied you, particularly with the increasing size of trial, it's almost mandatory to think of what extra you could do that would be plausible and useful.

Doll: I would like to confirm that because Peto, who carries out very large trials, always insists on having at least two treatments tested at once to make the best use of this very large amount of material.

Lennard-Jones: Could I comment on Sir Richard's trials as a bystander? I think there are several reasons for their success. Firstly, he had an end-point and this was the radiological end-point. He was able to measure the size of the ulcer in profile on barium meal. And, as I will be saying in a few moments, with duodenal ulcer this is not possible. Secondly, he was only referred patients with a proven gastric ulcer, so that he was able to concentrate entirely on this disorder and not be distracted by other things in outpatients; and he saw the patients in a small side room in the department. And the third reason for his great success was he did the trials himself and he saw all the patients and did everything himself. It was a recipe for an excellent trial.

Pounder: That's why everybody got better!

Hunter: I would like to make two points. First, this bland diet really did get around and it's not only in gastroenterological disease that it was used. Towards the end of the Second World War, President Franklin Delano Roosevelt became severely ill. A cardiologist diagnosed severe hypertensive heart disease with associated heart failure. As treatment he recommended that the President should have a bland diet and eat his meals on his own.

Secondly, could I reinforce what Professor Lennard-Jones has said about the simplicity of design of Sir Richard Doll's trials by using a historical example? Sir William Withering in his trial of digitalis leaf also adopted just one single criterion for entry into the trial – the presence of bilateral ankle oedema.¹³²

Pounder: Talking about trials, Sir Patrick Forrest, would you like to talk a bit about the surgical aspects of randomized trials?

Forrest: I went to Glasgow in 1954 and joined Charles Illingworth's department. Charles Illingworth had had a duodenal ulcer that had been treated by a partial gastrectomy. He had recognized at the time that Richard was carrying out his series of trials that a 'bland diet' did not help; he simply advised frequent small meals, alkali when required, and, if you liked milk, a glass of milk through the night when you got pain. If symptoms persisted surgery was the answer.

¹³² Dr Peter Hunter wrote: 'He also chose just one end-point, the disappearance of the ankle oedema and did the trial himself, studying 162 patients over nine years. This rigorous simplicity is one of the reasons his trial succeeded.' Fax to Dr Daphne Christie, 3 May 2002. See Roddis L H. (1936) William Withering and the introduction of digitalis into medical practice. *Annals of Medical History* 8: 93–112, 185–201. Aronson J K. (1985) *An Account of the Foxglove and its Medical Uses, 1785–1985*. London, New York: Oxford University Press.

The Peptic Ulcer Clinic in the Glasgow Western Infirmary was run by surgeons. We carried out the endoscopies using the Hermon Taylor gastroscope on a Friday (not a Saturday!)¹³³ afternoon and, of course, were responsible for surgical treatment. At that time nine gastrectomies were carried out each week in Illingworth's unit, comprising the first three operations on each of our weekly operation lists. Pulvertaft, in York, was dominant in drawing attention to the disastrous effects that gastrectomy could produce.¹³⁴ Even when it apparently went well as far as relief of symptoms was concerned, the problems of dumping, diarrhoea, anaemia and malabsorption kept the research interests of academic surgeons, including Michael Hobsley, fully occupied. Although by that time partial gastrectomy was standard surgical treatment for duodenal ulcer, we were still looking back to the apparent success of a simple operation of gastroenterostomy in Lord Moynihan's hands, his reported recurrent ulcer rate in 1000 patients being only 1.8 per cent. Eric Farquarson in Edinburgh had reviewed the results of five or six series, providing a total of 5000 cases, with a reported recurrence rate of 3.5 per cent.¹³⁵ However, the long-term follow-up of Glasgow cases reported by Douglas Clark put this at 30–40 per cent, which was much nearer the truth.¹³⁶ But there was still concern that 60 per cent of patients treated by this simple operation had long-term relief of symptoms and did not require more radical surgery. Douglas Clark and Andrew Kay in Glasgow, and Bill Small, Wilfred Card, Adam Smith and John Bruce in Edinburgh were attempting to select patients for gastroenterostomy on the basis of such factors as age, acid output and length of history, but this became irrelevant with the development of vagotomy.

In 1943 Dragstedt had reported the use of vagotomy to reduce acid secretion and relieve the symptoms of duodenal ulcer.¹³⁷ Although the operation had been used in Europe to relieve pain and vomiting in patients with *Tabes Dorsalis*, and six of Andre Latarjet's 24 patients had peptic ulcers, it was Dragstedt who introduced the operation on physiological principles and recognized that on account of gastric stasis, a drainage procedure was also required. Although Francis Moore, Surgeon-in-Chief at the Peter Bent Brigham Hospital in Boston, reported the successful use of vagotomy in 116 patients in 1948,¹³⁸ the operation was seldom used in Britain.

In 1954, when I went to Glasgow, Illingworth and Andrew Kay had decided to conduct a controlled randomized trial of the three surgical procedures then available to treat duodenal ulcer: partial gastrectomy, gastroenterostomy alone and

¹³³ This was said in respect of an earlier statement by Dr Hugh Baron that their gastroscopies were done on Saturday mornings (see page 47).

¹³⁴ Pulvertaft C N. (1964) The late results of gastric resection. *British Journal of Surgery* 51: 414–419.

¹³⁵ For a review of this work, see Johnson A G. (1983) Operations available for gastric ulcer: an overview, in Carter D C. (ed.) *Peptic Ulcer*. Edinburgh: Churchill Livingstone, 103–114.

¹³⁶ Clark D H. (1951) Posterior gastro-enterostomy in peptic ulcer: long term results. *British Medical Journal* i: 57–61.

¹³⁷ op. cit. note 63.

¹³⁸ Moore F D. (1948) Follow up of vagotomy in duodenal ulcer. *Gastroenterology* 11: 442–452. See also Moore F D. (1995) *A Miracle and a Privilege: Recounting a half century of surgical advance*. Washington, DC: Joseph Henry Press.

gastroenterostomy with vagotomy, and put their new lecturer in charge. We reported the initial results in 20 patients in each group to the British Society of Gastroenterology in 1958.¹³⁹ As in the gastroenterostomy-alone group there were seven recurrent ulcers we continued the trial, comparing only partial gastrectomy with vagotomy, and gastroenterostomy with 100 patients in each group. As Kay had gone to Sheffield, I to Cardiff, and Bill Burnett to Brisbane, the results of this trial, which showed little difference between the groups, were only reported in 1968 when Kay and Alan Cox had returned to Glasgow.¹⁴⁰

There is little doubt that the landmark trial of vagotomy in the UK was that conducted by Goligher and colleagues in Leeds. This included 375 male patients treated either by partial gastrectomy, vagotomy plus resection of the pyloric antrum and vagotomy with gastroenterostomy. Their report, at five to eight years of follow-up, showed little difference in the incidence of ulcer recurrence, but those patients treated by gastric resection had greater disturbance from dumping, those treated by vagotomy from diarrhoea.¹⁴¹ Although there were no deaths in the Leeds series, most British surgeons were regarding vagotomy as the safer procedure and gradually it replaced gastrectomy. But the incidence of diarrhoea caused great concern which over the years led to modifications of the standard ‘total’ vagotomy so as to avoid the need for a drainage procedure.

First came ‘selective vagotomy’ which spared the coeliac division of the posterior vagus supplying the liver and intestine. In London, Harold Burge was an enthusiastic supporter of this operation, claiming that gastric drainage was not required but this proved to be a false assumption. He also invented a pre-operative test to determine the completeness of the vagotomy, this involving the activation of a ring electrode around the lower oesophagus while monitoring intragastric pressure.¹⁴² Meantime pyloroplasty was superseding gastroenterostomy as a more physiological drainage procedure; and in 1969 James Kennedy and Alistair Connell in Belfast had reported in a randomized trial that selective and truncal vagotomy, both with a pyloroplasty, gave identical results.¹⁴³

Next, in 1969, came ‘highly selective’ or ‘parietal-cell’ vagotomy, which, by preserving the vagal nerve supply to the pyloric antrum, allowed its propulsive function to empty the stomach. David Johnston in Leeds was the prime proponent of this operation in the UK,

¹³⁹ Forrest A P M. (1958) The treatment of duodenal ulcer by gastroenterostomy, gastroenterostomy and vagotomy and partial gastrectomy. *Gastroenterology* 89: 307–311.

¹⁴⁰ Cox A G. (1971) Current trends in surgery for peptic ulcer, in Taylor S. (ed.) *Recent Advances in Surgery*. London: Churchill Livingstone, 46–68. See also op. cit. note 135.

¹⁴¹ Goligher J C, Pulvertaft C N, De Dombal F T, Conyers J H, Duthie H L, Feather D B, Latchmore A J, Shoemith J H, Smiddy F G, Willson-Pepper J. (1968) Five-to-eight year results of Leeds/York controlled trial of elective surgery for duodenal ulcer. *British Medical Journal* ii: 781–787.

¹⁴² Burge H, Vane J B. (1958) Method of testing for complete nerve section during vagotomy. *British Medical Journal* i: 615–618.

¹⁴³ Kennedy T, Connell A M. (1969) Selective or truncal vagotomy? A double-blind randomised controlled trial. *Lancet* i: 899–901.

reporting a large series of personal cases, but steadfastly refusing to conduct a randomized trial on the grounds that the results were so much better, particularly regarding reduction in the incidence of episodic diarrhoea.¹⁴⁴ The surgery of duodenal ulcer then settled down. Competent specialists adopted the ‘parietal-cell’ technique, but most general surgeons regarded truncal vagotomy and pyloroplasty as the more practical procedure.

The attitude in the USA was different. Whereas in the UK we were seeking the safest option, in the USA they wanted the operation that would give the highest rates of cure. Two large randomized trials were carried out, one by Paul Jordan in Houston, the other by the Veterans Administration, as a result of which vagotomy and antrectomy was regarded as the ‘gold standard’. It was widely practised in the USA, but on account of its greater mortality not in the UK.¹⁴⁵

Vagotomy and pyloroplasty was also being practised for gastric ulcer. Herbert Duthie in Sheffield reported a randomized trial in which he had compared vagotomy with the Billroth-I resection in which the gastric remnant was anastomosed to the duodenum. There was no difference regarding ulcer healing, but diarrhoea following vagotomy was a disadvantage.¹⁴⁶ However the trial, first reported in 1967, confirmed that vagotomy was an available option for those in whom gastrectomy was not technically feasible or posed too great a risk.

During this time there were also somewhat bizarre events. Wangensteen, in Minnesota, had designed a novel gastrectomy by which one removed a large proportion of the parietal-cell area of the stomach preserving the pyloric antrum.¹⁴⁷ Lloyd Nyhus, then working with Henry Harkins in Seattle, was spending a sabbatical year with Illingworth in Glasgow and persuaded me to carry out this operation on the premise that it reduced dumping. We performed the operation in eight patients only; the eighth patient was the last, for he had a massive haematemesis on his way home in the ambulance, which proved, on re-operation, to be due to a large chronic duodenal ulcer! The acid-inhibitory mechanism on gastrin release had clearly been too greatly disturbed.

Wangensteen’s next promotion, during the 1960s, was for ‘gastric freezing’ as a cure for duodenal ulcer.¹⁴⁸ On visiting him in Minneapolis, it did appear that the experimental

¹⁴⁴ See, for example, Johnston D, Goligher J C, Pulvertaft C N, Walker B E, Amdrup E, Jensen H E. (1972) The two- to four-year clinical results of highly selective vagotomy (parietal-cell vagotomy) without a drainage procedure for duodenal ulcer. *Gut* 13: 842.

¹⁴⁵ Jordan P H, Condon R E. (1970) A prospective evaluation of vagotomy-pyloroplasty and vagotomy-antrectomy for treatment of duodenal ulcer. *Annals of Surgery* 172: 547–560. Johnson W D, Grizzle J E, Postlethwait R W. (1970) Veterans Administration Cooperative Study of surgery for duodenal ulcer. I. Description and evaluation of method of randomization. *Archives of Surgery* 101: 391–395. Postlethwait R W. (1973) Five year follow-up results of operations for duodenal ulcer. *Surgery, Gynecology and Obstetrics* 137: 387–392.

¹⁴⁶ Duthie H L, Kwong N K. (1973) Vagotomy or gastrectomy for gastric ulcer. *British Medical Journal* iv: 79–81.

¹⁴⁷ Wangensteen H. (1952) Segmental gastric resection for peptic ulcer. Method permitting restoration of anatomic continuity. *Journal of the American Medical Association* 149: 18–23.

¹⁴⁸ Wangensteen O H. et al (1962) Achieving ‘physiologic gastrectomy’ by gastric freezing: preliminary report of experimental and clinical study. *Journal of the American Medical Association* 180: 439–444.

evidence on which it was based was somewhat slim, but patients were being treated – such as the farmer I met in the airport, who two days following his ‘freeze’ was returning to South Dakota. With MRC support we got a gastric freezing machine in Cardiff, and James Lawrie, who had perfected the histamine infusion test¹⁴⁹ to measure maximal acid secretion with our group, set about validating the procedure. After treating 13 patients, we concluded that gastric freezing was not a reliable or safe method of treating duodenal ulcer. Experimental work was indicating that a significant reduction in acid secretion only occurred with destruction of the gastric mucosa and the risk of necrosis of the gastric wall. Subsequently a randomized trial in humans was carried out at Duke University that compared actual with ‘sham’ freezing without demonstrable difference.¹⁵⁰

It was Hermon Taylor who in 1946 first advocated that perforated peptic ulcers should be managed conservatively, claiming that the results equalled those of surgical closure.¹⁵¹ From the results of a randomized trial in Cambridge,¹⁵² Brian Truscott, while showing little difference in outcome, came to the conclusion that, while having a place in management, conservative treatment was better reserved for the unfit and those in whom the diagnosis was in doubt.

Fortunately, in 1972, the scene changed with James Black’s development of H2 receptor antagonists.¹⁵³ Peptic ulcer was no longer a surgical disease, which, as far as the patient was concerned, was a far better deal!

Paulley: I just wanted to make a plea for more effort to be put into placebo effect in the various trials, particularly in the drug trials. Richard Doll has mentioned Morton Gill, who found that distilled water injections worked just as well as histidine injections, which were then the vogue for duodenal ulcer treatment in the 1930s.¹⁵⁴ Florey with Barry pointed out that this was probably psychologically based and Florey was usually right when he said things of that sort.¹⁵⁵ Quite by chance I came across a placebo effect while trying with a colleague to repeat Pickering and Bonney’s paper on acid and ulcer pain published in *Clinical Science* in 1946.¹⁵⁶ Ganglion-blocking drugs had just become available and we wanted to see if they would abolish ulcer pain

¹⁴⁹ Lawrie J H, Smith G M R, Forrest A P M. (1964) The histamine infusion test. *Lancet* ii: 270–273. See also Lawrie J H, Smith G M R, Goodall P, Pitman R G, Forrest A P M. (1965) Gastric freezing for duodenal ulcer. *British Journal of Surgery* 52: 226–230.

¹⁵⁰ Ruffin J M, Grizzle J E, Hightower N C, McHardy G, Shull H, Kirsner J B. (1969) A co-operative double-blind evaluation of gastric freezing in the treatment of duodenal ulcer. *New England Journal of Medicine* 284: 16–19.

¹⁵¹ Taylor H. (1946) Perforated peptic ulcer treated without operation *Lancet* ii: 441–444.

¹⁵² Truscott B McN, Withycombe J F R. (1950) Perforated peptic ulcer – an assessment of the value of non-operative treatment. *Lancet* i: 894–896.

¹⁵³ op. cit. note 125.

¹⁵⁴ op. cit. note 128.

¹⁵⁵ Barry H C, Florey H W. (1936) Histidine treatment of peptic ulcer. *Lancet* ii: 728–734.

¹⁵⁶ Bonney G L W, Pickering G W. (1946) Observations on mechanism of pain in ulcer of stomach and duodenum; nature of stimulus. *Clinical Science* 6: 63–89. *idem* (1946) Observations on mechanism of pain in ulcer of stomach and duodenum; location of pain nerve endings. *ibid.* 6: 91–111.

induced experimentally. We failed because patients with radiologically proven ulcers seen in the clinic and told that they would be admitted for the ‘acid’ test in a few days had lost their ulcer pain almost at once, and Bonney and Pickering’s protocol stated that the experimental subjects had to have experienced their ulcer pain spontaneously on the day of the test, which involved instillation of 100ml N/10 HCl into the stomach. It seemed, therefore, that being told that they would be admitted and have a test was enough to induce remission of pain.

So here is an example, like histidine mentioned earlier, of this point that with the intense medical attention received by some patients on complex investigative treatment regimens, placebo effect is likely to be considerable. Drug companies funding measurements of placebo effect should be aware that double-blind tricks with dummy tablets are not enough to exclude it!

Pounder: Thank you very much. As I joked with Sir Richard earlier, when you enter a clinical trial, you often get very, very good care and that may well be better than a placebo. As we will hear later, the placebo arms of the trials contain an enormous amount of information about the natural history of ulcer disease, and without the intervention of drugs.

One job that I have forgotten to do earlier in the day is to report that Sir Andrew Kay wasn’t well enough to come down here. He recorded a testimony to us, and I have got a transcript of this testimony. Just for the record and for interest I will tell you a bit of what he has to say about what has come to be called the ‘Kay test’.

The idea of its development. In 1950, I came across an article by Halpern who had been studying the pharmacodynamics of the new antihistamine drugs. Among other findings, he noted that the function of parietal cells was not inhibited by the drug.¹⁵⁷ I can still recall the excitement on having the notion that it might be possible to use an antihistamine to cover the systemic effects of increasing doses of histamine while pushing the parietal cells to the limit of their production of hydrochloric acid. Halpern had used guinea-pigs, I used myself, colleagues and volunteer patients. Throughout the study histamine was given subcutaneously in multiples of the usual bodyweight dose and systemic effects were covered by a prior injection of an antihistamine, mepyramine maleate. In this way a dose of histamine according to the subject’s body weight was achieved, which resulted in an output of hydrochloric acid that could not be augmented by giving more histamine. In this way a test was developed that produced a maximal response from the parietal cells; the duration of that response was then determined. Unlike its predecessors, this test had the advantage that replicate tests in one individual yielded consistently the same acid response. This is

¹⁵⁷ See, for example, Halpern B N, Maurice G. (1946) Etude quantitative de l’antagonisme de histamine et d’un antihistaminique de synthèse (antergan) sur l’intestin isolé de cobaye. *Compte Rendue Société de Biologie* 140: 830–832.

because the entire population of parietal cells present in the stomach had responded to a maximal stimulus. That the results of the test do, in fact, correlate closely with the total number of parietal cells, has been computed on the basis of laborious histological methods reported by Solly Marks in 1956, and by Wilfred Card and Marks in 1960.¹⁵⁸

During these studies I repeatedly wondered why the antihistamine did not block the action of histamine on the parietal cells. I got no further than asking the question and, like the rest of you, had to wait until Jim Black told us that it was all so simple, namely that there are two types of receptor! The H₂ antagonists, cimetidine and ranitidine, followed.

When the synthetic gastrin-like pentapeptide, pentagastrin, became commercially available, several surgical centres in the UK cooperated to determine whether pentagastrin would be a suitable alternative to histamine as a stimulus for maximal acid output.¹⁵⁹ A multicentre trial showed that it was and, being virtually free of side-effects, the pentagastrin test then replaced the augmented histamine test.

Thank you, Sir Andrew. Sir James, would you like to tell us the story of H₂ blockers? Sir James, as you may not have seen but you will all be very pleased to hear, has recently been invited to join the Order of Merit, which is indeed a great honour.

Black: I would like just to say to begin with is that all this today has been about remembering, and I will misquote Hilary Mantel now, who said, ‘Maybe there’s no such thing as memory, only the act of remembering. Remembering is about reconstruction as much as about recollection’.¹⁶⁰ So if, in fact, I am reconstructing history, I apologize. There was a little booklet on the history of H₂ antagonists some years ago¹⁶¹ and, after I read what everybody had said who had been there, I wrote an epilogue. The conclusion I came to is, ‘I was only certain of two things. I was there, and I wasn’t alone.’ So this business of remembering is quite difficult.

I would like to start off by telling you how, in 1964, I got into the H₂ receptor business. You have just had a very interesting account of the gastrin story from Graham Dockray. The gastrin saga started in 1905 when Edkins tried to do for the acid secretion what, famously, had been done three years earlier for the pancreatic

¹⁵⁸ Card W I, Marks I N. (1960) The relationship between the acid output of the stomach following ‘maximal’ histamine stimulation and the parietal cell mass. *Clinical Science* 19: 147–163.

¹⁵⁹ See, for example, Schmidt G, Petersen R A, Roszbach M, Hansky J, Ng S C. (1968) Pentagastrin as a gastric secretory stimulant. *Medical Journal of Australia* 2: 580–582. Wormsley K G. (1968) Pentagastrin stuff: a new means of stimulating gastric secretion. *Lancet* i: 57–58.

¹⁶⁰ Sir James Black wrote: ‘The quote comes from the *New York Review of Books*, 19 December 1996. A Review of *Alias Grace* by Margaret Atwood. The Reviewer was Hilary Mantel, under the title “Murder and Memory”.’ Letter to Dr Daphne Christie, 10 July 2002.

¹⁶¹ Smith Kline & French International Co. (1982) *The H₂-Receptor Anthology. The discovery of histamine H₂-receptors and their antagonists*. Welwyn Garden City: Smith Kline & French.

secretion by Bayliss and Starling. This was the discovery of the hormone ‘secretin’. Edkins made a neutral extract of the antral mucosa, filtered it, injected it into a vein, and got acid secretion. His control was to do the same thing for the body of the stomach and got no acid.¹⁶² He named the active ingredient ‘gastric secretin’, or ‘gastrin’. However, the secretin hypothesis was soon under attack by Popielski. He had made an acid extract of the duodenal mucosa and showed that it lowered blood pressure by producing widespread vasodilation. The same effect was seen with extracts of many other tissues. So he proposed that the active principle was ‘vasodilatin’ and, according to Barger and Dale,¹⁶³ Popielski claimed that the action of ‘secretin’ on pancreatic secretion was a ‘secondary and non-specific effect’. Barger and Dale also claimed that the active ingredient in Popielski’s ‘vasodilatin’ was most likely to be histamine. Then, in 1920, Popielski found that histamine was a potent stimulant of acid secretion.¹⁶⁴ This seemed to be the last nail in the coffin of Edkins’s ‘gastrin’. Eventually, in 1936, A C Ivy argues that gastrin *is* histamine.¹⁶⁵ However, a remarkable coincidence took place in 1938 in Babkin’s lab in Montreal. Babkin, a pupil of Pavlov, had become the doyen of North American gastroenterologists. Hank MacIntosh and S A Komarov were working in adjacent labs under Babkin’s direction. MacIntosh showed that gastric juice produced by vagal stimulation contained as much histamine as that produced by the infusion of histamine.¹⁶⁶ So he came to the conclusion that histamine is the final stimulant of acid secretion. In the lab next door, Komarov, using a different antral extraction procedure from Popielski’s, found that the solution could stimulate acid secretion although it was essentially free of histamine. Edkins’s gastrin was reborn. So 1938 was the year when everybody went chasing after gastrin, culminating in the brilliant work of Gregory and Kenner in Liverpool that Dockray reported earlier today.¹⁶⁷

However, where did my interest in histamine come from in the first place? A crucial period of my life was 1950–58, when I had the privilege of building a Physiology Department at the new University of Glasgow Veterinary School. There I had the

¹⁶² Edkins J S. (1906) The chemical mechanism of gastric secretion. *Journal of Physiology* 34: 133–144.

¹⁶³ Barger G, Dale H H. (1910–11) Chemical structure and sympathomimetic action of amines. *Journal of Physiology* 41: 19–59. *idem* Iminazolethylamine a depressor constituent of intestinal mucosa. *ibid.* 499–503

¹⁶⁴ Popielski L. (1920) Effect of tissue extracts on gastric secretion. *Pflügers Archiv* 178: 214–236, 237–259.

¹⁶⁵ See for example, *op. cit.* note 127, Chapter 2. Physiology, 21–45, in particular page 32.

¹⁶⁶ See, for example, MacIntosh F C. (1938) Histamine as a normal stimulant of gastric secretion. *Quarterly Journal of Experimental Physiology* 28: 87–98.

¹⁶⁷ See page 49. Professor Sir James Black wrote: ‘By 1964, when I set out to invent an H₂ receptor antagonist, no one was in any doubt that Edkins’s gastrin was the gastric hormone. However, there was considerable doubt about what, if any, was the physiological role of histamine. As late as 1971, L R Johnson wrote a paper [Johnson L R. (1971) Control of gastric secretion: no room for histamine? *Gastroenterology* 61: 106–118]. In the late 1950s and 1960s there were only two lone voices, C F Code and G Kahlson, who argued that gastrin stimulated the oxyntic cells indirectly by releasing histamine. The point is that, in 1964, there was simply not much interest in histamine as being physiologically relevant. I could not argue that the pursuit of an H₂ receptor antagonist would be a useful drug for the treatment of acid-related disorders, but I did argue that, at the very least, such a ligand would be a very useful tool for analysing the gastrin–histamine puzzle.’ Fax to Dr Daphne Christie, 31 May 2001.

good fortune of collaborating with two young surgeons from the Glasgow Western Infirmary. One, George Smith, an aspiring cardiac surgeon, trained by Claude Beck in Baltimore, was experimenting with hyperbaric oxygen to try to prevent post-occlusion ventricular fibrillation. This collaboration led me to develop my idea that, rather than trying to increase oxygen delivery to the heart, perhaps reducing cardiac oxygen demand would be equally effective. The invention of beta-receptor antagonists was the result. My other colleague was Adam Smith, a young gastroenterologist who had done postgraduate research with Feldberg at the National Institute for Medical Research.¹⁶⁸ Smith and I confirmed that 5-HT [5-hydroxytryptamine] not only stimulated mucus secretion (and emptied the colon!) but was also a potent inhibitor of histamine-stimulated acid secretion. The point is that this work with histamine meant that I knew that the antihistamines of the day would not inhibit histamine-stimulated secretion. That wasn't something new, it had been known since the early 1940s.¹⁶⁹

However, before leaving our discovery of 5-HT's ability to stimulate huge amounts of mucus secretion by the stomach, may I just point out that, so far today, there has been no reference to mucus secretion and its possible reference to peptic ulcer disease. This is odd because mucus has got considerable buffering capacity. The early observations by William Beaumont in 1833¹⁷⁰ on Alexis St Martin's chronic gastric fistula, emphasized the quantitative importance of the output of clear, clinging mucus. I know from personal experience that there are major technical difficulties in measuring mucus output. Whether it is relevant or not to the peptic ulcer problem, I don't know, but ignoring the problem seems a flawed strategy to me.

Now back to the main story. Between 1958 and 1964, while I was engaged with the beta-blocker programme, I became progressively fascinated by the parallelism between adrenaline antagonists and histamine antagonists. The most striking similarity, of course, was that just as the anti-adrenaline drugs could block some, but not all, of the actions of adrenaline, so the antihistamine drugs could block some, but not all, of the actions of histamine.¹⁷¹ So I decided that there was a histamine beta-receptor that deserved to have its antagonist. This is what we set out to do in 1964. However, some

¹⁶⁸ Professor Sir James Black wrote: 'He had found that when anaesthetized cats were treated with 5-HT, their stomachs were full of mucus.' Fax to Dr Daphne Christie, 31 May 2001.

¹⁶⁹ Loew E R, Chickering O. (1941) Gastric secretion in dogs treated with histamine antagonist, thymoxyethyl-diethylamine. *Proceedings of the Society for Experimental Biology and Medicine* 48: 65–68. See also Ash A S F, Schild H O. (1966) Receptors mediating some actions of histamine. *British Journal of Pharmacology* 27: 427–439.

¹⁷⁰ Beaumont W. (1833) *Experiments and Observations on the Gastric Juice, and the Physiology of Digestion*. Plattsburgh: F P Allen, 103–106. See also note 29.

¹⁷¹ Professor Sir James Black wrote: 'Ahlquist's dual adrenoceptor hypothesis had explained the selective antagonism by Fourneau's anti-adrenaline drugs and led the way to the invention of the beta-blockers. So, could a similar dual receptor hypothesis explain the selective antagonism of histamine's actions by Bover's antihistamines? Like, adrenaline, did histamine too have its beta-receptors? And there were other observations, such as different time courses of the refractory agonist responses.' Fax to Dr Daphne Christie, 31 May 2001.

years later, Ash and Schild showed that the histamine receptors that were sensitive to blockade were homogeneous across tissues and proposed that they should be classified as H1 receptors.¹⁷² So we were now looking for an H2 receptor antagonist.¹⁷³

I suppose I work a lot using analogies. In retrospect, the analogy between the pharmacology of histamine and adrenaline worked well for me. However, I took the analogy too far. Both of these substances, adrenaline and histamine, are very similar asymmetric molecules, derived from simple amino acids. They are both substituted ethylamines with different ring systems attached to the ethyl group. With the adrenaline story we started with Ahlquist's hypothesis that, when the N-methyl group in adrenaline is replaced by an N-isopropyl group, the compound, isoprenaline, becomes a highly selective agonist at beta receptors because it is no longer recognized by alpha receptors.¹⁷⁴

By analogy, I imagined that the efficacy of histamine would be a property of the imidazole ring and that the side chain N would contribute its affinity. And as it turned out, I was wrong. I was given a clue early on but I was so wedded to my analogy that I ignored it. We had put methyl groups into every substitutable position of the histamine molecule. One of these was on the fourth position of the imidazole ring, 4-methylhistamine (Appendix B, Figure 1). This compound had lost histamine's contractile activity on smooth muscle while retaining significant ability to stimulate acid secretion. I had discovered that 4-methylhistamine was to H2 receptors as isoprenaline was to beta receptors. Now that should have been the clue but I didn't read it. I should have said, 'If ring substitution makes a selective H2 agonist by losing affinity for H1 receptors, then substitution of the side chain N might lead to loss of

¹⁷² Ash A S, Schild H O. (1966) op. cit. note 169.

¹⁷³ Professor Sir James Black wrote: 'Let me remind you of the two major axioms of pharmacology that were discovered in the 1950s. Working independently, Stephenson and Ariens discovered that messenger molecules, hormones or neurotransmitters, behaved as though they had two non-contingent properties: a cognitive property of recognizing and binding to their conjugate cellular receptors, described as affinity; and a switching property of activating that receptor, described as efficacy. Explicitly, both investigators found that close analogues or derivatives of the native hormone (or messenger molecule) could exhibit partial loss of efficacy, which they have called partial agonists. The other axiom established by my guru, Professor Heinz Schild, was that molecules of quite different chemical structures could be shown, by model-directed methods, to belong to a single pharmacological class. This axiom has been the basis of the huge success of pharmaceutical research in the last 50 years.' Fax to Dr Daphne Christie, 31 May 2001.

¹⁷⁴ Professor Sir James Black wrote: 'Isoprenaline was introduced as an acute treatment for asthma. The drawbacks were cardiac stimulation, tachycardia and a very short duration of action. Powell and Slater [Eli Lilly (1958)] tried to deal with the latter problem by replacing the two hydroxyl groups on isoprenaline's phenyl ring with chlorine atoms, so-called dichloroisoprenaline or DCI. Unfortunately, for them, DCI had lost agonist properties on their *in vitro* bronchial muscle bioassay, and, with that, they lost interest in their bronchodilator programme. Then, within months, Moran and Perkins showed that DCI could block the effects of adrenaline on the contractile activity of heart muscle of the dog's heart. At ICI, my colleague, John Stephenson, immediately synthesized DCI, and on my bioassay, the guinea-pig Langendorff preparation, DCI was as potent an agonist as isoprenaline. This was my first encounter with the tissue dependence of partial agonists. Replacement of the dichlorophenyl ring with a naphthyl group led to a complete loss of all agonist activity and the first beta-blocker. What we had learned was that changing the substitution on the side chain N led to changes in affinity and changes in the ring substitutions led to efficacy changes.' Fax to Dr Daphne Christie, 31 May 2001.

efficacy and produce a selective antagonist' – but I didn't.¹⁷⁵ So it happened that the ninth molecule we made was a substitution of the side chain. In this compound a guanidino group replaced the terminal amino group. We tested this compound in the Ghosh and Schild preparation in which acid secretion was measured by lumen perfusion of the stomach of an anaesthetized rat. We found that this compound appeared to be as potent an agonist as histamine itself. This seemed to provide us with no lead and so it was put on the shelf. It took me over three years to find out that the guanido analogue of histamine was to H₂ receptors as dichloroisoprenaline was to beta receptors, namely a powerful partial agonist, a compound that had lost a small amount of histamine's efficacy. After that discovery the programme never looked back.¹⁷⁶

Booth: Sir James, I wonder if I could ask a question of great interest? You did this work in a commercial laboratory and one would like to know something about the attitude of the British pharmaceutical industry at this time. We know that Henry Wellcome before the First World War had employed Henry Dale as his first scientific director of his research laboratories. Did you have a tough time persuading tough commercial directors behind boardroom tables to let you work on this sort of thing?

Black: No. The industry, rightly sometimes, often gets a very bad press. But one thing where it gets an inadequate press is in the lengths to which it has been prepared to go to subsidize in-house research. There is no doubt in my mind that neither of the things for which I have got some notoriety could have been done with public money.

Pounder: And that's a key point.

Black: Not only as regards amount, but also particularly as regards duration.¹⁷⁷ Bear in mind that the commercial people at the top of these companies have to rely on the technical people at the bottom of the line for the ideas. They are not in a position to criticize the science. They have to take us on trust. What they are sensitive to is passion.

Pounder: Yes. That's very evident.

Danesh: I wish to reinforce what Sir James Black said in relation to mucus. John

¹⁷⁵ Professor Sir James Black wrote: 'Because of this blunder, Robin Ganellin and his chemists soldiered on for nearly four years making technically difficult changes to the imidazole end of histamine. During this time the discovery of the selectivity of 4-methylhistamine was the thin gruel that sustained my determination to keep going.' Fax to Dr Daphne Christie, 31 May 2001.

¹⁷⁶ Professor Sir James Black wrote: 'Burimamide, the prototype H₂ antagonist, was used for proof-of-principle studies in humans and metiamide and cimetidine followed in fairly quick succession.' Fax to Dr Daphne Christie, 31 May 2001. For chemical structures see Appendix B, Figure 3.

¹⁷⁷ Professor Sir James Black wrote: 'The beta-blocking programme was supported by ICI for six years and the H₂ antagonist programme was supported by SK&F [Smith Kline & French] for eight years. When I was at the Wellcome Foundation I was allowed to support Alistair Miller for over six years, work that led to lamotrigine for treating epilepsy. Johnson & Johnson have now been supporting me on a single project for over ten years. There's absolutely no way I would have got this degree of backing in the public sector. So my experience of four quite different pharmaceutical companies is that they, almost uniquely in science today, are prepared to take the long view. I think they deserve the credit for that.' Fax to Dr Daphne Christie, 31 May 2001.

Isenberg from San Diego, Wyn Rees and Leslie Turnberg from Manchester,¹⁷⁸ they all drew our attention to the mucus-bicarbonate barrier, as a mucosal protective layer. In 1986, in conjunction with the Department of Physiology in Glasgow, I pioneered the direct measurement of duodenal mucosal pH using a microelectrode endoscopically.¹⁷⁹ Compared with normal individuals, patients with duodenal ulcer disease despite maintaining a higher mucosal pH microclimate, were unable to neutralize fully the challenge of acid surge which was perfused through the endoscope.¹⁸⁰ This suggested that mucosal mucus-bicarbonate barrier is at a maximum drive in this disease. These findings support the influence of acid in causing metaplastic changes in the duodenal mucosa, and the role of rapid gastric emptying and the amount of acid produced in an individual patient in the pathogenesis of duodenal ulcer disease. We therefore should keep an open mind regarding the aetiological factors in this disease, as there are many people who carry *Helicobacter pylori* in their stomach and yet do not suffer from duodenal ulcer disease, and vice versa.

Pounder: The main proponent of mucosal defence couldn't come today – Lord Turnberg of Cheadle has sent his apologies. He would have spoken very eloquently for the bicarbonate side – for the opposition, so to speak. Shall we talk a bit more about the H2 antagonists and their early discovery? The very first experiments in humans were done at University College London by John Wyllie. Can you tell us about that study – there seemed to be a paper where your name was there, but I don't think you were a subject? I think otherwise almost all the others were subjects, weren't they?

Black: Yes. There were corporate objections to employees being subjects, but John Wyllie was a key player in the initial human studies. I have a slide that I used to show (Figure 8). There are two photographs of John sitting up in bed. On the left is shown John as the pale-faced Aberdonian that he is. On the right is shown him very red in the face with engorged conjunctivae because he is having histamine infused intravenously. There are two interesting points about these photographs. The first point is that he is red in the face in spite of the fact that he had been given a big dose of an antihistamine, enough to make him sleepy. And the second point is that the photo on the left was taken after the one on the right, after burimamide had been infused intravenously for 30 minutes.^{180a} This was the first time that we learned that histamine vasodilation involves both H1 and H2 receptors. [From the floor: He's got earphones on]. He had earphones

¹⁷⁸ Some of Lord Turnberg's work is described in Christie D A, Tansey E M. (eds) (2000) *Intestinal Absorption. Wellcome Witnesses to Twentieth Century Medicine*, vol. 8. London: The Wellcome Trust.

¹⁷⁹ Danesh B J Z, Lucas M L, Rawlings J M, Russell R I. (1986) The relation of gastric mucosal surface pH to luminal acid in gastric and duodenal ulcer patients. *Gut* 27: A1264. Rawlings J W, Danesh B J, Lucas M L, Morgan R J, Main A N, Russell R I. (1991) Gastroduodenal mucosal surface and luminal pH in gastric ulcer. *Digestive Diseases and Sciences* 36: 1543–1549.

¹⁸⁰ Danesh B J Z, Rawlings J M, Lucas M L, Russell R I. (1987) Capacity of the duodenal mucosal neutral pH-barrier to withstand acid challenge in health and disease in man. *Gastroenterology* 92: 1361–1362, *Gut* 28: A1405.

^{180a} Professor John Wyllie wrote: 'I seem to remember that I didn't ever have an infusion of burimamide, though I did have both metiamide and cimetidine. Anyway, the results would be the same.' Letter to Dr Daphne Christie, 10 August 2002.



Figure 8. John Wyllie as a key player in the initial human studies, showing him red in the face (darkened face, on the right) with engorged conjunctivae, following histamine infusion. Photograph provided by Sir James Black. Permission granted to reproduce photograph, Professor John Wyllie, 2002.

because behind him we had turned the side ward into a biochemical laboratory where we were measuring the blood levels of the antagonist every 20 minutes. So, there was a fearful racket going on behind him. Hence the head phones to soothe him with Bach.

Pounder: That was burimamide. How did you choose that as the target molecule, and why it was abandoned fairly rapidly soon after?

Black: Well, it was nothing other than a prototype. I don't think you can develop new drugs in one go. I think if you look at all successful programmes, there are prototypes that come out first that test the idea, and to give the company the confidence that investing huge amounts of money will pay off. The interesting feature about burimamide today is that it is rather weak as an antagonist of H₂ receptors, but it is a hundred times more potent as an antagonist of H₃ receptors. I missed that too!

Pounder: Metiamide then became available and one of the first people to investigate metiamide was George Misiewicz. Can you tell us about the experiments with Godfrey Milton-Thompson? The first experiment.

Misiewicz: Somebody said somewhere, 'There is a tide in the affairs of men' [**Booth:** It was Shakespeare, George],¹⁸¹ which means you have got to have a piece of luck to succeed, and I think I had several. I had several pieces of good luck, but I will just tell you about two. One was to attend a lecture on histamine H₂ receptor antagonists by the then Jim, now Sir James, which you [Sir James] gave at Hammersmith at about the time your paper came out in *Nature*,¹⁸² this attracted and excited me a great deal.

¹⁸¹ From William Shakespeare (1564–1616), *Julius Caesar*, Act 4, scene 3.

¹⁸² *op. cit.* note 125.

Another is to have some excellent colleagues. One of them was Roy Pounder, who was then a registrar at the Central. He is a genius at organizing things, and full of energy. Roy was going to do immunology. We were talking about it in the lab and I said to Roy, ‘Well, you can do immunology, it’s a very intellectual pursuit, but you will find it very difficult to get funding. But if you work in the gastric secretory field, you will be doing something of immediate practical importance and it won’t be difficult to get money to do the studies.’ So Roy made a decision and there we are.

The first studies we did were in collaboration with the Royal Naval Hospital in Haslar. This was because I got to know the head of gastroenterology there, Godfrey [now Sir Godfrey] Milton-Thomson – we met at St Mark’s Hospital, in Avery Jones’s clinic there. Initial studies were done with metiamide. We used a 24-hour, or overnight intragastric acidity technique, which we adapted from earlier work on diets by John Lennard-Jones and colleagues.¹⁸³ The metiamide studies were performed with David Jenkins and showed profound inhibition of nocturnal, or of stimulated, acid output. Then Roy [Pounder] came on the scene and we moved on to study the effect of cimetidine. We did these 24-hour gastric acidity studies on volunteers from the Navy. We always got our leg pulled about the ethical content of these trials, because people said, ‘Well, we know how it was, the command was issued: you, you and you are going to volunteer.’ But, in fact, these were extremely ethical experiments. We used paramedics, who really could give informed consent because they knew about medicine and in no way were they ordered to participate in those trials. Metiamide, as you know had to be withdrawn, because it produced leucopaenia. At that time, things perhaps weren’t as sophisticated as they are now, because I remember very well how we decided on the dose of cimetidine that was going to be studied clinically. There was no suggestion of doing dose-ranging studies, we sat round the table with the Smith Kline & French people, and we said well 200 mg, three times a day, and at night, seems about right doesn’t it? And everybody said yes and that was that. And that was how the dose was decided. In fact, we didn’t get it wrong. I remember, as if it were yesterday, the face of the first duodenal ulcer patient we treated with cimetidine. He had a severe ulcer. He had typical duodenal ulcer facies. Then he came back after having cimetidine treatment, and he was a completely different person, relaxed and pain free and happy looking – that made it all very worthwhile.

Pounder: I guess I will carry on with reminiscences of working with George. The interesting first clinical trial was with metiamide. George had shown that metiamide was a potent antisecretory drug.¹⁸⁴ So the idea was that we should start a double-blind placebo-controlled trial, to see what it would do in duodenal ulcer disease. In collaboration with the Royal Navy, we looked out for duodenal ulcer patients, we set up the trial, that was to be metiamide or placebo for eight weeks. We could not believe that you could persuade patients to have a second endoscopy. They were entered with

¹⁸³ op. cit. note 201.

¹⁸⁴ Milton-Thompson G J, Williams J G, Jenkins D J, Misiewicz J J. (1974) Inhibition of nocturnal acid secretion in duodenal ulcer by one oral dose of metiamide. *Lancet* i: 693–194.

an endoscopy, to prove they had an ulcer, and we then had very extensive symptomatic follow-up. We showed that the symptoms were settling in those that had the active drug and they essentially didn't settle very much in those that had placebo.

The other memory I have, is of the first experiment with cimetidine, when we were trying to work out the right dose. George's original experiment, done at night with metiamide, showed a dramatic decrease of acid secretion in every subject (op. cit. note 184). These were the first ulcer patients in the world to have a dose of cimetidine, double-blind (see Figures 9 and 10).¹⁸⁵ We were measuring their 24-hour acidity, and they were having active or placebo. We were measuring 'on the hoof' normal acidity, unlike stimulation tests with histamine and pentagastrin. So then we started the first 24-hour study. We were getting into the study and every hour on the hour, a sample of juice was taken from the stomach and acidity was measured with a pH probe. George, Godfrey, John Williams and me – sitting there, hour by hour. Then, 'There's acid here, Roy. What's going on? There's even more acid.' And they looked at me and said, 'What the hell are you doing, there's not supposed to be any acid'. We rang SK&F, 'Are you sure you have got the right tablets?'. 'Yes, yes'. They looked at me, 'Look at the box, did you give them the tablets?' And so the 24-hour profile was completed.

When the code was broken, there was a significant decrease of acidity with cimetidine, compared with the placebo, but it was nothing like knockout. And we spent a whole summer, I think we had even managed to get an abstract in somewhere, but we just couldn't explain the mild anti-secretory effect. I remember long conversations and wondering, 'What are we going to do? Why are these drugs not powerful in this situation?' And the answer I think is pretty simple in retrospect – that is, secretion stimulated by six meals a day, is a much, much more stringent target than the fasting secretion that sailors had had on the first occasion. So that was the start of cimetidine.

I worked with George [Misiewicz] for two years, from 1974 to 1976. I started at St Thomas' on Mayday of 1976. I was only the second non-St Thomas' person to be a medical senior registrar at the hospital. I went down this ward, a Nightingale Ward, behind the senior physician, John Anderson, a big man. Really like Sir Lancelot Spratt with the junior consultant, me as a senior registrar, the two registrars, sister, nurses, students, as we flew into the ward. It was my first ward round and my bleep went off and, being St Thomas' – it was quite a smart place in those days – the nurse went off and answered my bleep. She came back, she said, 'Excuse me, sir, there's a telephone call for you from New York'. Now telephone calls from New York in 1976 weren't every day, let alone in the middle of the senior physician's ward round. So I went to the phone and I remember this, a chap said, 'Hello, my name is Finkelstein (or something similar). I am from Wall Street, and I specialize in drug company stock'. 'Yes sir'. 'Tell me what you know about Smith Kline's Tagamet?' I said, 'Well, it's been in development for about a year'. He said, 'Tell me, does it heal ulcers?' I said, 'Yes,

¹⁸⁵ Pounder R E, Williams J G, Milton-Thompson G J, Misiewicz J J. (1975) 24-hour control of intragastric acidity by cimetidine in duodenal-ulcer patients. *Lancet* ii: 1069–1072.

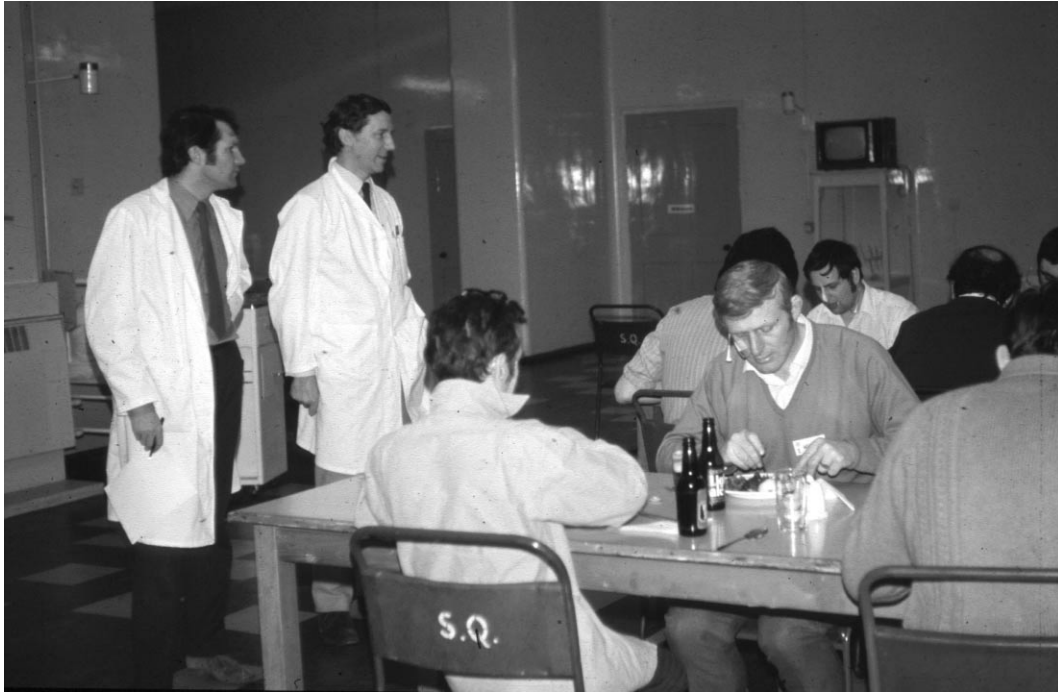


Figure 9. *The first duodenal ulcer patients in the world to receive a dose of cimetidine in 1975. The volunteers are on the right, supervised by Godfrey Milton-Thompson and John Williams, at the Royal Naval Hospital, Haslar (op. cit. note 185). Photograph provided by Professor Roy Pounder.*

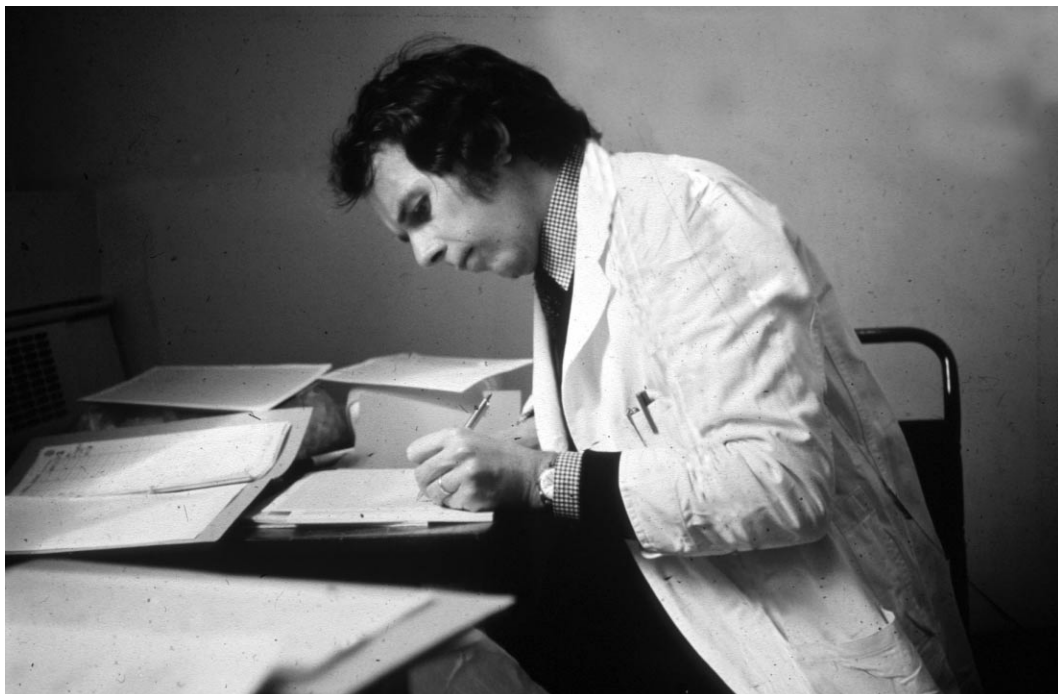


Figure 10. *Roy Pounder recording the results of the first 24-hour gastric acidity study, performed at the Royal Naval Hospital, Haslar, in 1975 (op. cit. note 185). Photograph provided by Professor Roy Pounder.*

about 80 per cent in four weeks have their ulcers healed'. He said, 'Tell me, do the ulcers come back?' I said, 'Yes. There are a few people who have their ulcers back'. He said, 'Do you think they are going to take the tablets for life?' I suddenly thought, 'By jove, he's right'. He, of course, bought shares, I never bought shares!

Until then, people looked upon H₂ antagonists as a cure for ulcer disease. Patients were very pleased when they got better at the end of one week, and came back in again after a month, 'Oh doctor, I feel marvellous'. They would come back two months later, having stopped them, saying, 'Doctor, your treatment's failed'.

I developed a mathematical model with jelly babies or Smarties to show people how the main benefit of antisecretory drugs was taking them as maintenance treatment (Figure 11).¹⁸⁶ So I was pretty involved in education and marketing. During this time my children were growing up; you will be pleased to know that the first word written by my eldest son was Tagamet. From the time he was born, every piece of paper he had to draw on had got Tagamet across the top of it! But I guess that's a good introduction to John Wood, who's with Glaxo Wellcome. He's going to tell us a bit about the commercial impact, what happened to the world after the development of the H₂ antagonists.

Wood: My interest in this field was really stimulated by three events. The first one was as a professional volunteer in Jack Hunt's laboratory at Guy's Hospital, and by sheer coincidence I saw someone today at this meeting that I hadn't seen for more than 30 years, who also used to swallow tubes in that laboratory. I spent about a year there, popping down a tube every day, 700 ml of fluid, with phenyl red to measure the gastric secretion, gastric emptying, and that was really my first interest in this area.

Secondly, James Black's paper in 1972 on the H₂ receptor¹⁸⁷ made a big impact on me when studying pharmacology at King's College in London. And the third event was having the opportunity to work in Los Angeles in Morton Grossman's laboratory, where there was a tremendous interest in this area. By coincidence, I was there in 1977 at exactly the time that Tagamet was being launched into the US market. Mort was chairing the large launch symposium that Smith Kline & French had organized for Tagamet, and as a research fellow of his I was invited as a guest. I nipped back to the lab at lunch time to pick something up, and Mort had also returned and was busy measuring up some figures of Jack Hunt's, in a *Journal of Physiology* paper, to check whether he thought the results were reliable! That was really a measure of this tremendous man.

I was asked to comment on the impact of H₂ receptor antagonists and I am going to divide this into four categories: Firstly the impact on patients and society; secondly the impact on gastric surgeons; thirdly the impact on the British pharmaceutical

¹⁸⁶ An army of jelly babies was used in lectures around the world by Roy Pounder, to explain a mathematical model of ulcer relapse and healing, demonstrating the benefit of maintenance treatment with an H₂ receptor antagonist. See Pounder R E. (1981) Model of medical treatment for duodenal ulcer. *Lancet* i: 29–30.

¹⁸⁷ op. cit. note 125.

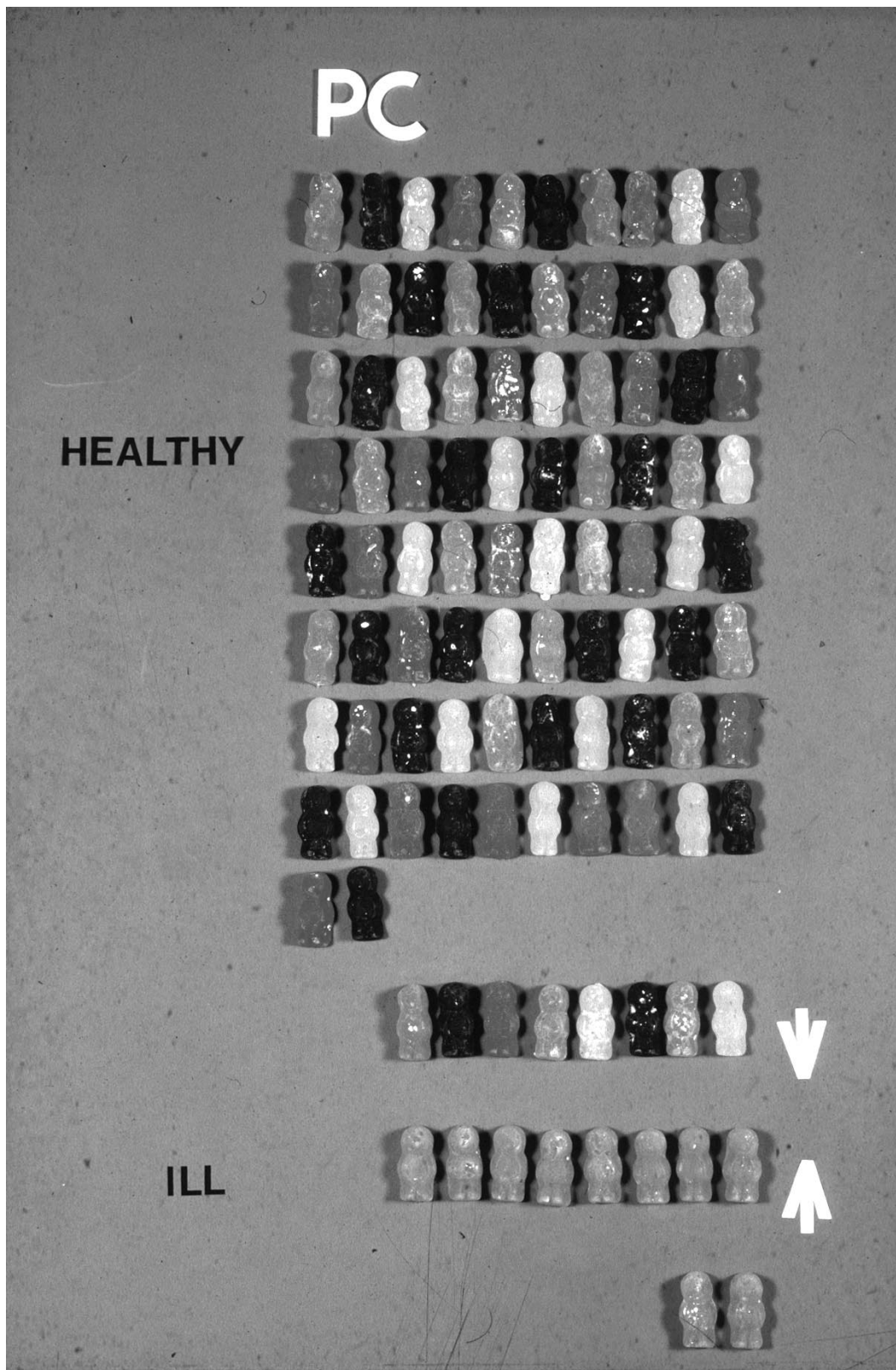


Figure 11. An army of jelly babies was used in lectures around the world by Roy Pounder, to explain a mathematical model of ulcer relapse and healing, demonstrating the benefit of maintenance treatment with an H₂ receptor antagonist (*op. cit.* note 186). PC = Placebo for maintenance treatment, and cimetidine for acute treatment – eight patients relapse and heal every month. Photograph provided by Professor Roy Pounder.

industry; and finally the impact on members of the audience here who have spent many years and hours and a large portion of their lives working in this area. So I'll start with patients and society.

I don't know how many patients have been treated with H₂ receptor antagonists, but when I spoke at an FDA hearing about five years ago, asking the US Food and Drug Administration [FDA] to give us approval to allow patients to prescribe this medicine for themselves, in other words to move it to over-the-counter status, at that time approximately 240 million patients had been treated with Zantac. Let's just make the assumption that about the same number were treated with Tagamet or famotidine (Pepcid). So you are talking about 500 million people that have received this category of drug, which is an enormous number. Of course these drugs have not only been used for peptic ulcer, but they have been used for reflux oesphagitis, and prevention of stress ulceration. One amusing anecdotal incident at a meeting in France, a Dutch gastroenterologist by the name of Henk Festen was sitting at the table with me and ate some tuna fish; felt quite unwell after lunch and became flushed. I had been reading some abstracts and papers on scombrototoxicity, which is a food poisoning due to consumption of fish of the scombrodriidae family. That's the mackerel and tuna family. If these fish are not transported properly, they generate huge amounts of histamine. I suddenly realized what was wrong with Henk and we searched around, and managed to get him an H₁ blocker from somebody who had some travel sickness pills. We also had an H₂ blocker and we treated him on the spot with both, and he got better. So that was quite gratifying.

Gastric surgeons I won't dwell on, but clearly the invention of this category of drug was good for patients but bad for senior surgical registrars who had spent a number of years training in all of the techniques that we heard from Professor Forrest in some detail earlier.

So moving on to the pharmaceutical industry. I am sorry James Black has had to leave the meeting early. He made a tremendous contribution to British pharmacology and the British pharmaceutical industry, both during his time at ICI and also when he worked for Smith Kline & French. Tagamet made an enormous contribution to patients' lives. I have spent about 15 years of my life working on trials and on other studies with ranitidine, and the newspapers used to portray us as adversaries and I guess indeed we were adversaries. Ironically, we are now about to merge, Glaxo Wellcome and Smith Kline Beecham,¹⁸⁸ over the next few weeks, but in those days we were competitors and we conducted a large number of studies to compare the relative benefits of Tagamet and Zantac. Zantac eventually took over from Tagamet as the leading drug on a global basis being prescribed for the treatment of peptic ulcer and stayed up there as the world's top-selling ethical pharmaceutical for 11 years, which is quite an achievement. At the peak of its sales, the drug was selling to £2.3 billion per annum on a global basis. This is a huge amount of money. The total

¹⁸⁸ Glaxo Wellcome and Smith Kline Beecham merged to form GlaxoSmithKline on 27 December 2000. Details can be found at www.gsk.com/about/mergerinfo.htm (site visited, May 2002).

amount of money generated by the product would exceed something like £20 billion on a lifetime basis. And the question is what has happened to that money and that's really one of the impacts of these drugs. Essentially I see the money as having gone in various directions. First it went to shareholders, that's your pension funds, so I think you all did pretty well out of it. And secondly it was ploughed back into research, so, for example, the building of the Glaxo Wellcome Research Centre at Stevenage was the second largest building project in Europe after the Channel Tunnel, an enormous endeavour. And this research, where money is being spent at the moment at the rate, just for Glaxo Wellcome, of about £1.3 billion a year to find new drugs, culminated in new drugs for migraine, asthma, and several new drugs for the treatment of AIDS. So the huge amounts of money generated from H2 receptor antagonist sales have been recycled back into drug development, as James Black alluded, in search of new medicines across a wide variety of diseases.

I just wanted to talk about the comments made earlier regarding placebo.¹⁸⁹ We do take placebo results very seriously in the pharmaceutical industry. In fact all of our new drugs are developed in large-scale, placebo-controlled trials, and so not only does the drug have to be effective, it has to be more effective than the placebo effect, and that's a very important thing, so you don't leave this room with any misapprehensions. Indeed, placebo-controlled trials are mandatory for approval of new drugs.

Finally, just to touch on members of the audience. Several have spent a lot of their time travelling the world, talking about this category of drugs, and doing a lot of research in terms of trials and so I think it is probably true that these drugs have touched many of our lives in the audience.

Pounder: I think the placebo aspect of these trials is very interesting, because the development of the H2 antagonists coincided with the widespread introduction of endoscopy. For the first time we had a real record of, for example, the rate of recurrence of ulcer disease. We had people who were followed up for a year and they were seen very regularly and very rigorously; they were endoscoped when they got symptoms, or endoscoped at six months and a year. We showed that people were getting recurrent ulceration, we showed what was happening during maintenance, so that a lot was learned about the natural history of ulcer disease.

McColl: I think one of the other very important things that the introduction of the H2 antagonist showed us, perhaps more in retrospect, was a further insight into the aetiology of the duodenal ulcers. There was a study by Richardson that looked at 24-hour acid output in duodenal ulcer patients, control patients, and duodenal patients on a standard dose of cimetidine.¹⁹⁰ What he showed was that cimetidine was bringing the

¹⁸⁹ See Dr John Paulley's comments, page 61.

¹⁹⁰ Richardson C T, Walsh J H, Hicks M I. (1976) The effect of cimetidine, a new histamine H2-receptor antagonist, on meal-stimulated acid secretion, serum gastrin, and gastric emptying in patients with duodenal ulcer. *Gastroenterology* 71: 19–23. op. cit. note 207.

24-hour acid output in the duodenal ulcer patients back to normal levels. We also knew that this dose of cimetidine healed the duodenal ulcer. I think this gave us the evidence that increased acid secretion was a key factor in the aetiology of the duodenal ulcers.

Pounder: An important point that comes from that is that controlling acid secretion doesn't heal ulcers directly – it produces an environment in which the ulcers can heal. So maybe it's a bit pedantic, but I think it is important.

Baron: If I could just amplify McColl's point that before we had such data for H₂ blockers, we had good data from the surgical operations which Pat Forrest discussed. It isn't the different operations that produced different results, it is entirely a factor of the percentage inhibition of acid achieved by the operation. There is a strict direct correlation between the success of any surgical operation (success meaning non-recurrence) and the percentage reduction of peak acid output.¹⁹¹ There are excellent data, for example, from Denmark, that it is a combination of the acid reduction of the operation and the pre-operative acid output.¹⁹² You get bad results from vagotomy if you are operating on somebody with a peak acid output of 60 mmol/h, because even if you achieve the necessary object of an operation, 67 per cent reduction, you will not get it down to safe levels. Unfortunately different surgeons, with the same operation of vagotomy, were achieving a wide range in reduction of acid output. It was only if they could get acid down below 20 mmol/h that there would be no recurrence. The same remarks would, of course, apply to all other acid inhibitors from antacid to prostaglandins, through anticholinergics, through H₂ blockers to proton-pump inhibitors.¹⁹³ All medical and surgical acid-lowering treatments fall on the line with the meta-analyses done by Richard Hunt at McMaster University, Hamilton, Ontario.¹⁹⁴

The other point I would like to make historically, with the greatest respect to John Isenberg and to the newly ennobled Professor Turnberg, is that the people who should be honoured for the mucus and mucosal bicarbonate barrier are Franklin Hollander and Horace Davenport.¹⁹⁵ They defined these particular defences, but their problem was, 'But we don't know how to stimulate such defences'. Hollander therefore went on to look for appropriate acid inhibitors.¹⁹⁶ He got good results with anticholinergics (which we seem to have discussed very little, presumably because of their side-effects) but there were excellent controlled trials of anticholinergics both in America and in

¹⁹¹ Baron J H. (1994) The history of acid inhibition. *Yale Journal of Biology and Medicine* 24: 21–36.

¹⁹² Baron J H. (1978) *Clinical Test of Gastric Secretion. History, methodology and interpretation*. London: Macmillan Press.

¹⁹³ Baron J H. (1997) Peptic ulcer: a problem almost solved. *Journal of the Royal College of Physicians* 3: 510–520.

¹⁹⁴ Jones D B, Howden C W, Burget D W, Kerr G D, Hunt R H. (1987) Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with anti-secretory drugs. *Gut* 28: 1120–1127.

¹⁹⁵ Davenport H W. (1939) Gastric carbonic anhydrase. *Journal of Physiology* 97: 32–43. *idem* (1943) Secretion of acid by gastric mucosa. *Gastroenterology* 1: 383–389. Hollander F. (1950) *Secretion of Gastric Mucus*. Philadelphia: W B Saunders. See also Sidebotham R L, Baron J H. (1994) Franklin Hollander: the two-component mucous barrier. *Gastroenterology International* 5: 135–140. Werther J L. (2000) The gastric mucosal barrier. *Mount Sinai Journal of Medicine* 67: 41–53.

¹⁹⁶ Baron J H. (2000) Treatments of peptic ulcer. *Mount Sinai Journal of Medicine* 67: 63–67.

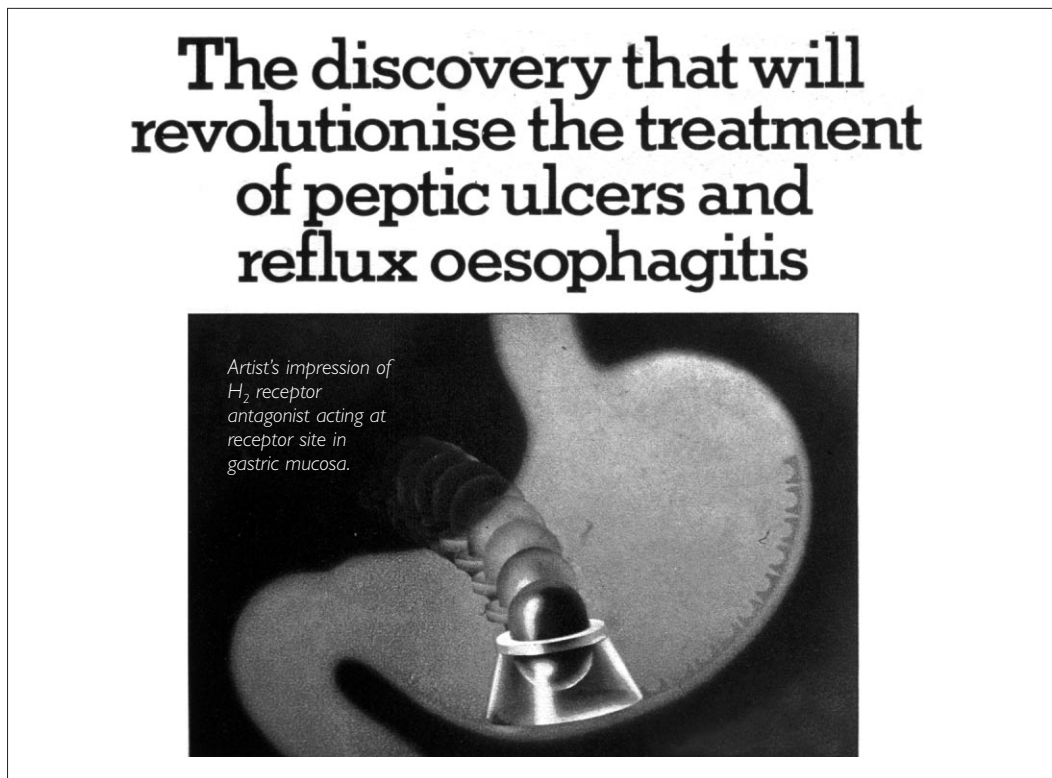


Figure 12. The first advertisement for a histamine H₂ receptor antagonist, in November 1976, Smith Kline & French, Welwyn Garden City, Herts. Photograph provided by Professor Roy Pounder.

Sweden, which showed how effective they were, given for years, as you were saying, Mr Chairman, by keeping acid levels safely low.¹⁹⁷

The final point I want to make is about Smith Kline & French. We know about their brilliant scientists, but they also deserve great credit for their marketing department. As I said at the beginning of this meeting, you had to overcome the antipathy of British doctors to the role of acid. Their marketing, I think, was directed by a man who had been marketing director of a cosmetic firm. Their beautiful pictures of H₂ receptors, and the blockers, and the stimulatory effect, were sufficient to cause British doctors to prescribe it in the hundreds of millions of which we have heard from John Wood (See, for example, Figure 12). It was a major paradigm shift for doctors to be told that histamine stimulates receptors on the acid-producing parietal cells and that these receptors can be blocked, all in the pretty pictures, like your jelly babies, Chairman (Figure 11).

Doll: I am sorry this is going back to the early period in trials. Firstly, I want to thank John Lennard-Jones for pointing out that the success of our trials had been because we were able to measure the size of the reduction of the ulcer. That was because of the radiologist, Frank Pygott, who personally X-rayed all the patients at the beginning and end of the trial, and got them into a position in which you had the maximum silhouette of the ulcer. So it was Frank Pygott's contribution that enabled us to get at all accurate reductions in the size of the ulcer.

¹⁹⁷ Baron J H. (1983) The pharmacology of gastric acid. *Scandinavian Journal of Gastroenterology* 18: 7–23.

The second thing I wanted to say is quite separate. Talking earlier about jejunostomy and how it was successful in so many patients we also tried to think how we could find the patients for whom jejunostomy might be an adequate, cheap and effective treatment. It's a very simple operation and we found in reviewing several hundred jejunal ulcers from many clinics that they were most common in non-secretor blood group O patients. So we said, 'Ah, here's the answer'. We just do this operation for people with blood group A and B, who are secretors. Peter Gummer agreed to do this operation on those people with duodenal ulcers, but many of them got jejunal ulcers, as they had done with this operation in the past, so that didn't work.

The third thing is a historical anecdote, which I think is specifically for Christopher [Booth], but it is of some general interest, because it does reflect the attitudes to diet at the time. This was during the war, and Captain Cleave, a naval doctor, was the doctor for the home fleet at Scapa Flow, and he believed in treating peptic ulcers by giving people steaks and baked potatoes and roast apples. Those were the characteristic items of his diet. Well, the Admiral came to see him one day with typical duodenal ulcer symptoms, he had him X-rayed, and the Admiral had a big duodenal ulcer. He said, 'I am sorry, Admiral, you will have to come into hospital, there's no alternative, to let this ulcer heal'. Well, the Admiral agreed. Two hours later he came back and he said, 'I am sorry I am not going into hospital, the Bismarck has put to sea and we are going after it'. So he went after it. Captain Cleave said, 'OK, on condition that you have my diet, you have steak and baked potatoes and roast apples and wholemeal bread' and the Admiral was very happy to agree to that condition. Well, as you know, eventually the German battleship was sunk, but not before a very considerable proportion of the British Navy was also sunk. When he returned back to Scapa Flow, Captain Cleave had him X-rayed and his duodenal ulcer had healed. I think that is significant, both in relation to the dietary treatment of ulcer and the effects of psychosomatic stress.

Pounder: Oh well, admirals are a very relaxed kind of people. John Lennard-Jones wants to talk a little bit more about the treatments that were available just before the H2 antagonists, which he researched while he was at the Central Middlesex.

Lennard-Jones: I feel like somebody out of the ark after all the description of H2 blockers. I, in fact, got out of research into peptic ulcers when H2 blockers came in. This was a deliberate decision on my part, because I could see that the whole scene was changing and, in fact, my research interests by that time were elsewhere. But for some years in the 1950s and 1960s I devoted practically all my research, or a lot of my research interests, to peptic ulcer.

If I may, I will take you back to the 1950s again, because in the 1950s we did realize that acid was very important. We had seen the work of Cox¹⁹⁸ in 1952, who showed

¹⁹⁸ Cox A J. (1952) Stomach size and its relation to chronic peptic ulcer. *American Medical Association Archives of Pathology* 54: 407–422.

that duodenal ulcer was associated with an increased parietal-cell mass. We knew of the work of Andrew Kay,¹⁹⁹ we knew that there was an increased maximal histamine output in patients with duodenal ulcer and we knew of the correlation between that test and the parietal-cell count. I got intrigued with the question of diet, not just simply the Sippy diet and the Lenhartz diet,²⁰⁰ but I was interested to see whether the different proportions of the diet might be relevant. I did some experiments in which I gave equicaloric diets, but with different ratios of protein and carbohydrate, but constant fat to see the effect on 24-hour acidity in the stomach. After we had lunch today, the acidity in our stomach has fallen because it has been buffered by protein and then it rises steadily, until just before tea. I was intrigued that perhaps protein has two effects; it has a buffering effect and a stimulant effect. The proportions of the diet in fact made no difference to the acidity in the stomach. I also studied frequency of feeding as opposed to infrequent feeding, again with equicaloric meals and found that frequent feeding does have some effect, because it smoothes out the peaks of high acidity.²⁰¹ This work took me some years and I got involved with anticholinergics, which were the only antisecretory drugs of that time. The ganglion blocker, C6 hexamethonium, was studied by Rowlands and his colleagues in 1952.²⁰² I went on to study a drug called Poldine and showed that it did indeed show demonstrable reduction in acidity in the stomach in people taking food, but the reduction was very slight, and I did a controlled therapeutic trial, which failed to show any benefit.²⁰³ This work led me into the whole business of controlled trials in duodenal ulcer, which is why I envied Sir Richard Doll the end-point of the area of the gastric ulcer crater, because we couldn't do that at the time in duodenal ulcer.

In 1967, I was invited to the American Gastroenterological Association [AGA] to review the whole problem of controlled trials in duodenal ulcer. We were reliant on days of pain, days off work, severity of pain, daytime pain, night-time pain, and patient's opinion, rather than radiology, and this made trials very difficult. The whole situation changed radically in the early 1970s, when endoscopy gave us an end-point

¹⁹⁹ Kay A W. (1953) op. cit. note 4. See also page 62.

²⁰⁰ Lenhartz's diet consisted mainly of eggs (eight given daily, four boiled and four raw) with other foods soon added to ensure a generous intake. Sippy relied mainly on milk, to which eggs and other bland foodstuffs were added after the lapse of several days. See Lenhartz H. (1904) Eine neue behandlung des ulcus ventriculi. *Deutsche Medizinische Wochenschrift* 30: 412. Sippy B W. (1915) Gastric and duodenal ulcer: medical cure by an efficient removal of gastric juice corrosion. *Journal of the American Medical Association* 64: 1625–1630. Wosika P H, Emery E S. (1935) The effectiveness of the Sippy regimen in neutralizing the gastric juice of patients if the amount of alkali is not varied. *Annals of Internal Medicine* 9: 1070–1077.

²⁰¹ Lennard-Jones J E, Barbouris N. (1965) Effect of different foods on the acidity of the gastric contents in patients with duodenal ulcer. Part I. A comparison between two 'therapeutic' diets and freely-chosen meals. *Gut* 6: 113–117. Lennard-Jones J E, Fletcher J, Shaw D G. (1968) Effect of different foods on the acidity of the gastric contents in patients with duodenal ulcer. Part III. Effect of altering the proportions of protein and carbohydrate. *ibid.* 9: 177–182.

²⁰² Rowlands E N, Wolff H H, Atkinson M. (1952) Clinical assessment of drugs which inhibit gastric secretion with special reference to hexamethonium. *Lancet* ii: 1154–1158.

²⁰³ Lennard-Jones J E. (1961) Experimental and clinical observations on poldine in treatment of duodenal ulcer. *British Medical Journal* i: 1071–1076.

in duodenal ulcer and the H2 blockers came in to give us a completely new antisecretory treatment.

But in the meantime, it's just worth recording that some other treatments were mooted. We regarded as important the concept of a balance between aggressive effect of acid and pepsin and the defensive forces of mucus and the alkali secretion and perhaps epithelial cell turnover in the stomach. To attempt reduction of acid, we studied anticholinergics as I have told you. I also got involved with the idea of gastric freezing, and I went with Sir Herbert Duthie to America to see Dr Wangensteen²⁰⁴ and observe this new technique in Minneapolis and New York. I also visited Charles Frederick Code and others at the Mayo Clinic – where experimental work on the topic had been done. The only research I have ever done in dogs was on gastric freezing, and it showed that it was necessary to damage the mucosa to reduce acid secretion. The degree of damage depended on the temperature within the balloon and the pressure with which it was applied, and if the temperature was too low and the pressure was too great then you got a deep ulcer.²⁰⁵ So this was clearly not a treatment for humans.

In 1974, from Edinburgh, there came an interesting paper on gastric irradiation for reducing gastric hydrochloric acid secretion.²⁰⁶ They did this in elderly patients who had very troublesome ulcers, but who were not suitable for surgery, and it was in fact effective.

It is intriguing that antacids were tried on their own and there was an excellent trial in 1977 from America, which showed that if you took enough antacids, you could heal duodenal ulcers.²⁰⁷ The problem was the amount of antacid you had to take; though later trials showed that such large doses were not necessary. From a mucosal defensive aspect, it is intriguing that in 1965 there was a trial of bismuth aluminate.²⁰⁸ This was a sequential trial, and you will remember that a sequential trial depends on which one of a pair does better than the other. The authors showed with only six pairs that bismuth aluminate was better than magnesium trisilicate and they made measurements in the stomach and showed that it did not affect the amount of pepsin in the gastric juice or the pH. So there was a little pointer about bismuth 16 years before another trial suggested that a bismuth compound decreased the relapse rate in duodenal ulcer.²⁰⁹

²⁰⁴ Peter E T, Bernstein E F, Sosin H, Madsen A J, Walder A I, Wangensteen O H. (1962) Technique of gastric freezing in the treatment of duodenal ulcer. *Journal of the American Medical Association* 181: 760–764. op cit. note 148. See also page 60.

²⁰⁵ Lennard-Jones J E, Smith T, Farrer-Brown G, Peduzzi R D. (1966) Observations on the temperature causing mucosal damage in the dog during gastric freezing. *Gut* 7: 535–541.

²⁰⁶ Findlay J M, Newaishy G A, Sircus W, McManus J P. (1974) Role of gastric irradiation in management of peptic ulceration and oesophagitis. *British Medical Journal* iii: 769–771.

²⁰⁷ Peterson W L, Sturdevant R A, Frankl H D, Richardson C T, Isenberg J I, Elashoff J D, Sones J Q, Gross R A, McCallum R W, Fordtran J S. (1977) Healing of duodenal ulcer with an antacid regimen. *New England Journal of Medicine* 297: 341–345.

²⁰⁸ Matts S G F, Swan C H J, Kelleher J. (1965) Double-blind trial of bismuth aluminate and magnesium trisilicate in peptic ulceration with simultaneous gastric analysis. *British Medical Journal* i: 753–756.

²⁰⁹ Martin D F, Hollanders D, May S J, Ravenscroft M M, Tweedle D E, Miller J P. (1981) Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. *Lancet* i: 7–10.

The other studies that perhaps are worth mentioning were Truelove's trials of oestrogens for men with duodenal ulcer in 1960.²¹⁰ This caused a considerable stir, but nobody took it up, which was not surprising because it was not an acceptable treatment. Later, in the 1980s, came prostaglandins, again with the idea of increasing mucosal protection. They do decrease acid secretion but they also have a protective influence. Their effect on healing, while demonstrable, was so much less than the H2 blockers that they never really took off,²¹¹ although they are used sometimes, I think, with non-steroidal anti-inflammatory drugs.

Pounder: And there are one or two other interesting things that I would add to that. One was the story of enprostil, a prostaglandin analogue.²¹² It turned out that it had two isomers, one of which was active and one inactive; and the chemists produced these isomers in random amounts, so there were some capsules that had active stuff in them and some hadn't, depending on the batch number. They had even more trouble because the dose was 50µg, but getting 50µg into every capsule proved impossible, so some had 1000µg but the next 19 capsules had nothing in at all.

The next interesting thing to remember was one leading article, probably written, I almost suspect, by Hugh Baron.²¹³ It was when the *Lancet* had unnamed leading articles, where it was dubbed 'anticholinergic drugs might be called logical placebos?' Perhaps it was Langman that did it, I can't tell. The other one, which Hugh Baron didn't write, was published in 1948, in the *British Medical Journal*.²¹⁴ There was a review about antihistamines, and noting how the histamine stimulates gastric acid secretion,

It is strange that on gastric secretion alone there has till now been no suggestion of antagonism between substances [histamine and the anti-histamines] which are antagonists everywhere else. It is likely there is some simple explanation of this anomaly, which should well repay exploration.

The final thing, for the record, I think we should mention, is that Britain performed the first double-blind placebo-controlled, endoscopically controlled trial of duodenal ulcer. This was done in Bristol, with Paul Brown, Paul Salmon and Alan Read, where they were testing carbenoxolone as Duogastrone in 1972.²¹⁵ They had a double-blind placebo- and endoscopically-controlled trial to show that Duogastrone speeded the healing of ulcers, and I think that was a first for the world.

²¹⁰ Truelove S C. (1960) Stilboestrol, phenobarbitone, and diet in chronic duodenal ulcer. A factorial therapeutic trial. *British Medical Journal* ii: 559–566.

²¹¹ Hawkey C J, Walt R P. (1986) Prostaglandins for peptic ulcer: a promise unfulfilled. *Lancet* ii: 1084–1087.

²¹² Developed by Syntex Research, Palo Alto, California, USA. See Thomson A B. (1986) Treatment of duodenal ulcer with enprostil, a synthetic prostaglandin E2 analogue. *American Journal of Medicine* 81: 59–63. See also page 123.

²¹³ Anonymous. (1970) Anticholinergics and duodenal ulcer. *Lancet* ii: 1173.

²¹⁴ Anonymous. (1948) Antihistamine drugs and gastric secretion. *British Medical Journal* ii: 1028.

²¹⁵ Brown P, Salmon P R, Htut T, Read A E. (1972) Double-blind trial of carbenoxolone sodium capsules in duodenal ulcer therapy, based on endoscopic diagnosis and follow-up. *British Medical Journal* iii: 661–664.

Tovey: Talking about mucosal protection, I think mention should be made of sucralfate. I remember visiting Michael Moshal in Durban in 1980, at the time when he was using sucralfate and when he published his paper asking, ‘Does the duodenal mucosa change?’²¹⁶ At that time sucralfate was being used very largely throughout Asia and there was no doubt that the healing results were the same as with H₂ antagonists, and the relapse rate was very much less.²¹⁷ We looked into that ourselves and we gave cimetidine for one-year maintenance, sucralfate for one-year maintenance; the cimetidine ones had a high relapse rate, the sucralfate ones did not. We were looking at duodenal gastric metaplasia; the cimetidine ones had the same amount of metaplasia as at the beginning and the sucralfate ones had considerably less.

Pounder: Well, there’s a whole family of Japanese ‘mucosal protectors’ which are clearly active. I guess part of it is that the H₂ antagonists, and the proton-pump inhibitors, had such a clear story to tell doctors. If you ask how the sucralfate works, you have a list of about 16 different explanations.

McColl: I think that a key reason why the sucralfate and also the bismuth agent, Denol, healed ulcers is because they both markedly reduce the density of *H. pylori* infection.²¹⁸ Of course at the time that these drugs were found to be effective in healing ulcers we were unaware of the presence or significance of *H. pylori* infection.

Celestin: Just a short piece of history regarding metiamide. We put 32 patients on metiamide in an open trial indefinitely and the thirtieth one showed leucopaenia. At the time SK&F felt that it couldn’t be due to their drug and that it could have been due to a viral infection. But they allowed the patient to come off the metiamide and be rechallenged. This produced a massive leucopaenia that ended the era of metiamide. But it wasn’t a disaster, because what happened when we stopped all treatment (and these were the days before the 1981 Human Rights Act of Helsinki)²¹⁹ the patients agreed to continue having endoscopies, while not on any treatment. Within six months every ulcer had recurred, showing that the H₂ receptor antagonist

²¹⁶ Moshal M G, Gregory M A, Pillay C, Spitaels J M. (1979) Does the duodenal cell ever return to normal? A comparison between treatment with cimetidine and denol. *Scandinavian Journal of Gastroenterology Supplement* 54: 48–51. Moshal M G, Spitaels J M, Khan F. (1980) Sucralfate in the treatment of duodenal ulcers: a double-blind endoscopically controlled trial. *South African Medical Journal* 3: 742–744.

²¹⁷ See, for example, Dhali G K, Garg P K, Sharma M P. (1999) Role of anti-*Helicobacter pylori* treatment in *H. pylori*-positive and cytoprotective drugs in *H. pylori*-negative, non-ulcer dyspepsia: results of a randomized, double blind, controlled trial in Asian Indians. *Journal of Gastroenterology and Hepatology* 14: 523–528.

²¹⁸ Wagstaff A J, Benfield P, Monk J P. (1988) Colloidal bismuth subcitrate. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in peptic ulcer disease. *Drugs* 36: 132–157. Lee S P. (1991) The mode of action of colloidal bismuth subcitrate. *Scandinavian Journal of Gastroenterology* 185: 1–6. See, for example, Marshall B J. (1991) The use of bismuth in gastroenterology: the ACG Committee on FDA-Related Matters. *American College of Gastroenterology* 86: 16–25. See also Banerjee S, El-Omar E, Mowat A, Ardill J E, Park R H, Watson W, Beattie A D, McColl K E. (1996) Sucralfate suppresses *Helicobacter pylori* infection and reduces gastric acid secretion by 50 per cent in patients with duodenal ulcer. *Gastroenterology* 110: 717–724.

²¹⁹ Howard-Jones N. (1982) Human experimentation in historical and ethical perspectives. *Social Science and Medicine* 16: 1429–1448.

had not altered the natural history of the disorder. But it also showed another feature: that as the ulcers recurred many patients had no symptoms. Michael Moshal showed this in a much larger series in Durban.²²⁰ So we then knew that many patients were going around with ulcers without symptoms at all, and this showed how unreliable were all forms of trials where endoscopy had not been used before.

Pounder: Six hundred patients were given metiamide and six developed agranulocytosis. There's a lot of histamine in the bone marrow, without a very clear role, and so there was a worry, or a potential problem, that H₂ blockade was something to do with cell maturation. The critical experiment was done by Duncan Colin-Jones in Portsmouth.²²¹ He had a patient with a Zollinger–Ellison syndrome who was on metiamide, whose life was being saved and controlled, an impossible situation. That patient was switched directly from metiamide to cimetidine very early on in cimetidine's life. That patient's acid remained controlled, and the bone marrow recovered while under H₂ blockade. There was a day when H₂ blockers might have died, but for that bit of experience.

Baron: I am glad John Lennard-Jones mentioned irradiation, but the Edinburgh study was uncontrolled and the Australian study showed some renal damage from the irradiation so it never really took off.²²² However, the long-term American studies showed a clear correlation as with any other medical or surgical acid-lowering treatment, that those whose acid came back to where they started from got the recurrences and those whose acids stayed low, didn't.²²³

The other historical point is to give the credit to Franklin Hollander again, to look at ways of lowering acid and classify them into extracellular (namely antacids) surface receptor blockers, and because of their limited success, the future must lie in intracellular blockers. He was influenced even before the war by the concept that acid was produced in the parietal cell by carbonic anhydrase splitting H₂O into the hydrogen ion coming out into the lumen as acid and bicarbonate coming back into the blood stream. Hollander chose to use acetazolamide that was a powerful carbonic anhydrase blocker. And it didn't work, mainly because the physiology was wrong.²²⁴ We now know from Forte and Sachs's work that the intracellular enzyme is H⁺, K⁺ ATPase.²²⁵ The theory was right, it was just that the facts were wrong!

Pounder: Would you like to carry on, and introduce proton-pump inhibitors (Figure 13)?

²²⁰ Bremner C G, Hinder R, Segal I, Moshal M G, Spitaels J M, Wright J P, Laage N J, van de Merwe C F. (1982) Endoscopic experiences in the Republic of South Africa. *Gastrointestinal Endoscopy* 28: 258–260.

²²¹ See Burland W L, Sharpe P C, Colin-Jones D G, Turnbull P R G, Bowskill P. (1975) Reversal of metiamide-induced agranulocytosis during treatment with cimetidine. *Lancet* ii: 1085.

²²² op. cit. note 206.

²²³ Palmer W L. (ed.) (1974) *Gastric Irradiation in Peptic Ulcer*. Chicago, London: University of Chicago Press.

²²⁴ Baron J H. (2000) Treatments of peptic ulcer. *Mount Sinai Journal of Medicine* 67: 63–67, in particular page 66.

²²⁵ Sachs G, Chang H H, Rabon E, Schackman R, Lewin M, Saccomani G. (1976) A non-electrogenic H⁺ pump in plasma membranes of hog stomach. *Journal of Biochemistry* 251: 7690–7698.

Baron: If you get your enzyme right, everything else will follow. Any pharmaceutical company should be able to produce a drug that will block any particular enzyme, and they did. It was perfectly possible for me to advise Astra that if their proton-pump inhibitor would inhibit 97 per cent of acid, it would heal 97 per cent of ulcers. And it did. And on Richard Hunt's analysis graph it's as simple as that.²²⁶

Pounder: Again, it's an acute treatment and, if you stop taking it, people go back to square one.

Baron: Well, that's just the point you were making, Chairman. It heals the ulcer but it's not a long-term cure of ulcer disease.

Paulley: I rather gathered that somebody here had the brazenness to say that endoscopy had produced a beneficial effect in itself. A speaker here a moment ago said there was a good period after endoscopy. Is that correct?

Pounder: No. They got better while waiting for endoscopy, but he was saying that everybody got their ulcers back.

Paulley: They got their ulcers back but they didn't get the pain. So the pain wasn't there, but they did get their ulcers back. I was just going to say that it appears that endoscopy might have been therapeutic. That's really why I talked about placebo.²²⁷ There were two trials among medical students in the USA,²²⁸ one of them got a rise in ulcer and one got a fall, but it all depended on who was doing the test, it sometimes comes down to which gender operator is involved. If it is a female operator, it may go up, if it's a male, it may go down. It's the same with blood pressure. I was just trying to ask for more attention to the baseline of the placebo, not only the double-blind. I am sure the double-blind stuff is all right, but that's not the same thing as what's going on as well.

Pounder: I shall leave that as a speculation for Mike Langman. There is one teaching hospital in London that has the world's lowest placebo healing rate for ulcers.²²⁹ You will find the answer when you read the transcript of the Witness Seminar, or you can ask Professor Northfield.

Langman: We ought to refer to the pharmaceutical industry's success in producing drugs that were safe. If you look back to 1976, the then medical director of SK & F, William Burland, decided he needed a study of a large number of people. Duncan Colin-Jones, Martin Vessey, David Lawson and I, recruited 10 000 takers and followed them and we published the last paper last year, about 20 years after we

²²⁶ See page 77 and op. cit. note 194.

²²⁷ See note 128.

²²⁸ Wolf S. (1982) Psychosocial forces and neural mechanisms in disease: defining the question and collecting the evidence. *Johns Hopkins Medical Journal* 150: 95–100.

²²⁹ St George's Hospital, London. See Blackwood W S, Maudgal D P, Pickard R G, Lawrence D, Northfield T C. (1976) op. cit. note 126.



Figure 13. Some of the first duodenal ulcer patients in the world to receive doses of omeprazole (a PPI) at the Royal Free Hospital, London, in 1981. Photograph provided by Professor Roy Pounder. © Professor Roy Pounder, 2002.

started.²³⁰ At this time there were no PCs, all the analysis was done by John Beresford on a mainframe IBM computer at night, because management thought that what it usually did was much more important than looking at drug safety at that time. It turned out to be very useful, because there was passion expended for some years at the British Society of Gastroenterology about the risks of developing gastric cancer because of acid secretory inhibition; it turned out that any tumours diagnosed were likely to have been present all the time. I think we owe a debt to the industry for funding our work, and I remember well one sentence in our presentation that ended, ‘This study gives some reassurance about the safety of cimetidine’. It was early on and I had no idea of what ‘some’ meant at that stage.

Pounder: This final session is really devoted to *Helicobacter pylori*. Stewart Goodwin is going to tell us the real secrets about where it all started.

²³⁰ See, for example, Colin-Jones D G, Langman M J, Lawson D H, Logan R F, Paterson K R, Vessey M P. (1992) Postmarketing surveillance of the safety of cimetidine: 10 years mortality report. *Gut* 33: 1280–1284.

SESSION 4: **HELICOBACTER PYLORI**

Goodwin: My first experience of peptic ulceration research was as Chairman of the Ethics Committee at Northwick Park Hospital in 1973 and 1974. David Tyrrell was the Scientific Committee Chairman when Jonathan Levi asked to study cimetidine. Fortunately the Ethics Committee approved. In 1973 I had been invited to lecture all over Australia on antibiotics and in 1975 I was invited to work in Perth; that is how I, a Britisher, came to be working in that beautiful city in Western Australia.

I would just like to set the scene by reading two sentences from a paper submitted to *Gut* in May 1983, which was a month before Marshall and Warren put their letters into the *Lancet*.²³¹ It was a paper on duodenal ulceration:

Bacteria are related only to the surface of gastric-type epithelial cells. Whether these cells are located at areas of gastric metaplasia and the duodenal bulb, or in the pre-pyloric region of the stomach, the bacteria are not associated with the surface of intestinal type epithelial cells. The bacteria are absent from the biopsies of those patients with a normal stomach and duodenum.²³²

Warren is always rather reluctant to admit that other histopathologists besides him were equally aware of these spiral bacteria; it was Rollason in Birmingham, who had looked at 310 endoscopic gastric biopsies and found bacteria in 42 per cent of cases.²³³ So in 1981 there were several people round the world who knew about these bacteria. Of course there were many more before that, but for the purposes of our talk this afternoon, I will try to restrict you to that. And so it was that in 1981 in the Royal Perth Hospital, which is a 1000-bed hospital in Western Australia, there was the histopathologist, Warren, who had been seeing these spiral bacteria, and there was a junior registrar, called Marshall, who was doing a rotation in gastroenterology. He got very interested in these bacteria and he came up to my department and started asking some of my technicians to try to grow biopsies, without success. Then, in October, he realized that he needed to do a proper study. He came to me and we devised a protocol with 100 patients and the consultant gastroenterologists, Tom Waters and Chris Sanderson, took the biopsies and Marshall (as I have described in my paper in *Gut* in 1993) was what I call the catalyst.²³⁴ Marshall certainly was extremely energetic. He read very widely, and he wrote one or two really good papers.

²³¹ Warren J R. (1983) Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* **i**: 1273. Marshall B. (1983) *ibid.* 1273–1275.

²³² Steer H W. (1984) Surface morphology of the gastroduodenal mucosa in duodenal ulceration. *Gut* **25**: 1203–1210.

²³³ Rollason T P, Stone J, Rhodes J M. (1984) Spiral organisms in endoscopic biopsies of the human stomach. *Journal of Clinical Pathology* **37**: 23–26.

²³⁴ Goodwin C S. (1993) *Helicobacter pylori*: 10th anniversary of its culture in April 1982. *Gut* **34**: 293–294.

Anyway, let's just go back to October 1981, when he came to me and asked me if we could grow these organisms. I was in charge of a department of 55 members, the microbiology department, and I put in charge of this project my number 2, John Pearman, who is now Head of the Department. At the time we were trying to combat a methicillin-resistant *Staphylococcus aureus* epidemic²³⁵ (and I kept it out of the State for the next 15 years). So this was just a minor request. Marshall had no money, and I wonder whether if he had gone to somebody in the USA and said, 'Please will you try to grow these organisms, but I have got no money', whether he would have got very far. Anyway, I was quite prepared to help him. I had been helped as a junior myself in leprosy work and other things, and so we started in March. I am afraid to say that whenever he writes about these things, with regard to the dates and to the people, he nearly always gets them wrong.

In any case the study started in March 1982 and Barry has said that we didn't grow the organism from the first 34 cultures, because we weren't terribly good at microaerophilic *Campylobacter* culture. Well, it isn't true. In fact, it's not true to say that *Campylobacters* are the same as *Helicobacter* that I named later. *Campylobacters* grow at 42°C. *Helicobacter* grows at 37°C so we weren't looking only for *Campylobacters*. John Pearman, in charge of the project, has told me and we haven't published it, that there were various parameters we were looking at. If you leave cultures in for more than two days, they tend to get overgrown, certainly by the fourth day. It was really very fortunate that not only the Australian Easter holiday came in April 1982, but also that the culture plate was not overgrown, so that when we turned up after the long Easter holiday, we had the first culture on 14 April 1982.²³⁶ It was from a lady aged 62 years, Eileen, I had better not tell you her surname, it began with C. She had a large gastric ulcer and a healed duodenal ulcer. I was very fortunate to have in my department an expert PhD, Doug Annear (who also has not had enough credit), and from her isolate he immediately desiccated this organism, lyophilized not freeze-dried, because it doesn't survive freeze-drying. He desiccated and preserved it; in fact, it is not the one that Barry will tell you about, 11637, it's 11638,²³⁷ because 11637, which is now the commonest worldwide culture, certainly in the National Collection of Type Cultures here, and also in the USA, came from an isolate in May. During that study of 100 patients, I said for 34 we did not culture it, we saw it on the Gram stain and then we cultured it from another 12 patients.

Barry then went off to his next rotation, which was in Port Hedland, with his wife and four children; he had the children quite young. He looked at all the patients' notes in great detail and realized that in every case of duodenal ulcer we had cultured the

²³⁵ Pearman J W, Christiansen K J, Annear D I, Goodwin C S, Metcalf C, Donovan F P, Mace K L, Bassette L D, Powell I M, Green J M. (1985) Control of methicillin-resistant *Staphylococcus aureus* (MRSA) in an Australian metropolitan teaching hospital complex. *Medical Journal of Australia* 142: 103–108.

²³⁶ op. cit. note 242.

²³⁷ op. cit. note 242.

organism, and of course it was most highly related to active, that is polymorph-containing, gastritis. He came back to Perth in 1983 and went to Fremantle Hospital, WA, where he worked as a microbiology registrar, not doing any microbiology except in *H. pylori*. He started a clinic with a very cooperative gastroenterologist there, Ian Hyslop, and they produced a very fine paper in 1985, on the first big series of patients, isolation and incidence. Meanwhile, I went on sabbatical leave – I suppose it's the most costly sabbatical leave I have ever been on – and he sent the letter to the *Lancet*²³⁸ and also wrote his paper with Warren for the *Lancet* in 1984.²³⁹ You may be interested to know why, for the first two letters in the *Lancet* in May 1983, Warren and Marshall didn't write a joint letter? Warren is very difficult to agree with on any text; I have had several papers I have never published, because he couldn't agree on the final text. Armstrong was an eminent electron microscopist there and he said, 'Well, why don't you publish two letters?' So they did, the first under Warren and the second under Marshall.²⁴⁰

And the story of the first culture led on, of course, to many other things. People round the world in many other centres immediately started isolating the organism. Barry himself came to London, and there was a *Campylobacter* conference and Martin Skirrow proposed the name *Campylobacter pyloridis*, although it was published in our first paper.²⁴¹ You don't get names of bacteria just by publishing them in any old journal, you have to send it to the *International Journal of Systematic Bacteriology* (IJSB). So when I wrote the paper in 1984 on the original isolation, in a rather obscure journal *Microbios Letters*,²⁴² I sent that paper to IJSB and the name was validated finally in 1985.²⁴³ As Roy [Pounder], I believe, shows on one of his lecture slides, we got the grammar wrong and so I changed it to *Campylobacter pylori*.²⁴⁴

The other story, of course, is how did the name *Helicobacter* arise? Well, I was a bacteriologist, Barry had gone off to America, and he wasn't interested in bacteriology anyway. We worked very hard for about four years with many aspects of generic features – I won't go into detail, because it's all bacteriology. Anyway I sent it to the *International Journal of Systematic Bacteriology* and they accepted my new genus name

²³⁸ op. cit. note 231.

²³⁹ Marshall B J, Warren J R. (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* i: 1311–1315.

²⁴⁰ op. cit. note 231. See also Kidd M, Modlin I M. (1998) A century of *Helicobacter pylori*. Paradigms lost – paradigms regained. *Digestion* 59: 1–15. Allan P. (2001) What's the story *H. pylori*? *Lancet* 357: 694. Marshall B J. (2002) *Helicobacter Pioneers: First hand accounts from the scientists who discovered Helicobacter, 1892–1982*. Melbourne: Blackwell Science Asia.

²⁴¹ op. cit. note 242.

²⁴² Marshall B J, Royce H, Annear D I, Goodwin C S, Pearman C J W, Warren J R, Armstrong J A. (1984) Original isolation of *Campylobacter pyloridis* from human gastric mucosa. *Microbios Letters* 25: 83–88.

²⁴³ See Goodwin C S, McCulloch R K, Armstrong J A, Wee S H. (1985) Unusual cellular fatty acids and distinctive ultrastructure in a new spiral bacterium (*Campylobacter pyloridis*) from the human gastric mucosa. *Journal of Medical Microbiology* 19: 257–267.

²⁴⁴ Marshall B J, Goodwin C S. (1987) Revised nomenclature of *Campylobacter pyloridis*. *International Journal of Systematic Bacteriology* 37: 68.

of *Helicobacter*.²⁴⁵ We now have 19 named species in the genus, and many others.²⁴⁶

Booth: As I understand it the story is precisely as you described it, but would you like to comment on the work that Marshall did on attempting to prove Koch's postulates? Where was that published? As I see it, that was one of the most significant pieces of work.

Goodwin: Absolutely. These were the two papers he published from that hospital. He tried to inoculate pigs. That went wrong, and he finally decided to inoculate himself. I think that he was very brave, and he tried once and he failed, he didn't get any symptoms. Then he was endoscoped by Hyslop and found to have a normal gastric mucosa. He swallowed a new three-day culture, felt very unwell and they did another endoscopy, which was extremely uncomfortable. They found the organism, and grew it, and that was the successful proof of Koch's postulates, which he published.²⁴⁷ They are published next to each other in the *Medical Journal of Australia*,²⁴⁸ Barry's paper was called pyloric *Campylobacter* and it was an absolutely first-class paper. As I say I will go on later and talk about the papers that we did together, about the pathogenesis.

I would just like to mention John Armstrong, the electron microscopist, for if you are going to prove that *H. pylori* is important in stomach disease, you have to prove what the lesions are. This was published for the first time in 1986 in a paper I wrote with John Armstrong (and with Barry Marshall's biopsies) showing the specific electron microscopic changes in the stomach; and also showing the improvement after antibiotics with reversal of these specific lesions.²⁴⁹ We also started a double-blind placebo-controlled study giving antibiotic or cimetidine. Colm Ó'Moráin's study was published first and we managed to get ours in December 1988. Also included in that issue of the *Lancet* was the paper on the 'leaking roof' concept in which I wrote the first fully referenced explanation of how *H. pylori* is necessary but not sufficient for duodenal ulceration.²⁵⁰

²⁴⁵ Goodwin C S, Armstrong J A, Chilvers T, Peters M, Collins M D, Sly L, McConnell W, Harper W E S. (1989) Transfer of *Campylobacter pylori* and *Campylobacter mustelae* to *Helicobacter* gen. nov. as *Helicobacter pylori* comb. nov. and *Helicobacter mustelae* comb. nov. respectively. *International Journal of Systematic Bacteriology* 39: 397–405. Goodwin C S. (1989) *Campylobacter pylori* becomes *Helicobacter pylori*. *Lancet* ii: 1019–1020.

²⁴⁶ For a history on *Helicobacter pylori* see, for example, Dooley C P. (1993) Background and historical considerations of *Helicobacter pylori*. *Gastroenterology Clinics of North America* 22: 1–4. See also Fox J G. (2002) The non-*H. pylori* helicobacters: their expanding role in gastrointestinal and systemic diseases. *Gut* 50: 273–283. See also op. cit. note 240.

²⁴⁷ See Marshall B J, Armstrong J A, McGeachie D B, Glancy R J. (1985) Attempt to fulfil Koch's postulates for pyloric *Campylobacter*. *Medical Journal of Australia* 142: 436–439.

²⁴⁸ op. cit. note 40.

²⁴⁹ Goodwin C S, Armstrong J A, Marshall B J. (1986) *Campylobacter pyloridis*, gastritis, and peptic ulceration. *Journal of Clinical Pathology* 39: 353–365.

²⁵⁰ Humphreys H, Bourke S, Dooley C, McKenna D, Power B, Keane C T, Sweeney E C, Ó'Moráin C. (1988) Effect of treatment on *Campylobacter pylori* in peptic disease: a randomised prospective trial. *Gut* 29: 279–283. Marshall B J, Goodwin C S, Warren J R, Murray R, Blincow E D, Blackbourn S J, Phillips M, Waters T E, Sanderson C R. (1988) Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* ii: 1437–1442. Goodwin C S. (1988) Duodenal ulcer, *Campylobacter pylori*, and the 'leaking roof' concept. *ibid.* 1467–1469.

Pounder: Can I just have a follow-up to that? Were any of you in Perth at that time aware of John Fordtran's study of transmissible gastritis, in his work from Dallas?

Goodwin: We had some ideas on that, from Barry Marshall. I am a mere bacteriologist. I can't answer for him, but he read very widely and mentioned various other papers.

Pounder: Those transmissible infections were identified in retrospect. Colm, you have been mentioned. Tell us about how you embraced this germ, and your original study.

O'Morain: Sir Christopher Booth had a very big influence in my career. I qualified in Dublin in 1972 in medicine and did the usual registrar's jobs around Dublin and got my Membership. I was very fortunate in getting a job in France with Jean Pierre Delmont, who had an interest in rugby. I got a sport scholarship playing scrum-half for Nice University. Jean Pierre is a friend of Christopher Booth and pioneered endoscopy in France,²⁵¹ and unlike us in Britain and Ireland, they had the foresight of inviting over the Japanese experts to teach them how to do endoscopy, so they were further advanced in endoscopy than the UK and Ireland. I benefited from this work and I went back to Ireland, and was immediately seized on, got a great signing-on fee, but soon got fed up being a junior doctor in Ireland and applied for a job in Northwick Park, where Sir Christopher was the Director. I heard the opposition I was against, one was a chap called Walter Melieux, who subsequently joined the British army and has been promoted upwards. I rang my classmate and said, 'What's this chap Walter Melieux like?' 'Well, if he's applied for the job, I wouldn't bother applying'. So I went with trepidation for the interview. James Neuberger was another applicant, and Christine Swinson. I was sitting outside; Sir Christopher and the great and late Jonathan Levi, were the interviewers. Sir Christopher said, 'James, how's your father?'²⁵² I thought, 'What chance do I have of getting this job?' But when I went in Sir Christopher asked me all about rugby and France and foie gras, and I, of course, got the job and that really has influenced me greatly.

Every Friday Sir Christopher would bring the juniors into his office and pour out the sherry and over sherry he told me once that he was a republican socialist. Coming from Ireland, I wondered what sort of subversive organization he belonged to – but he reassured me and we had some great times there, and as I mentioned, Jonathan Levi, who had a great influence in my clinical career, was a superb clinician and really is deeply missed. He used a drug called Denol, a bismuth preparation, in the treatment of ulcers. I was brought up at a time, like most of us around here, we dined out on free lunches, and cimetidine or Smith Kline & French were the first words our children learnt in the year of 1976 onwards. But Jonathan always believed Denol to be a better drug than cimetidine and treated all duodenal ulcers with Denol. At the time it was a

²⁵¹ See, for example, Delmont J, Dumas R. (1985) Endoscopic treatment of 83 cases of post-cholecystectomy choledochal lithiasis. *Minerva Chirurgica* 40: 483–488.

²⁵² James Neuberger was the son of Professor Albert Neuberger CBE FRCP FRS FRSC, Professor of Chemical Pathology, St Mary's Hospital, University of London, 1955–1973.

liquid form and I took this on board, and I tell this just because it is a terrible smelling medicine – the patient believed in it, and got better. One of the patients that I dealt with in Northwick Park was a brother of the Managing Director of Smith Kline & French in Dublin. So when I went back eventually to Dublin after a time in New York, I met the Managing Director. He said, ‘You treated my brother when you were in Northwick Park, I was fed up sending him free samples of Tagamet. After he was treated with Denol, he never needed Tagamet again’. There was published literature showing Denol to be superior to Tagamet, particularly in long-term studies.²⁵³ And I took this on board and read the letters that Stewart [Goodwin] mentioned in the *Lancet* from Perth, from Barry Marshall and Robin Warren. This impressed me and opened up a new era, I think, for us as gastroenterologists – collaboration with pathologists and microbiologists. So, I was fortunate enough to have junior registrars who had a foot in each camp in pathology and microbiology, and my own registrar at the time, and we decided to see if Denol, which was a known bismuth preparation, had antibacterial properties. You could take biopsies before and after, and randomize, it was a single-centre study, we would randomize each successive patient either to Tagamet or to Denol. And we found that, of course, Tagamet healed the ulcer. Four weeks after the treatment we did a further endoscopy and Denol also healed ulcers.

One of the deficiencies we were taught in our training in the UK at the time was that most research was done in six months, because our contracts were usually for six months. In fact, I remember Sir Christopher saying, ‘You have only got six more months in Northwick Park and you are out’. So every research project was done in six months and nobody would do anything longer. I said I would break this mode, we would give it a year. So we brought back the patients in a year. The difficulty about this was that the registrar who was the first-named person on the paper in the *Lancet* in 1987,²⁵⁴ Gerry Coghlan – a most unlikely doctor, in fact he looked more like a coal miner, maybe a milkman. We had great difficulty getting the patients back and so we had to invite them, phone them up, and they still wouldn’t come back. Gerry himself would go round to their houses, provide a taxi, to bring them back for their repeat endoscopy one year later.²⁵⁵ And when he knocked at their door, the fellow came out, and he thought it might be the milkman, because they noticed over that year, when their ulcer was cured as opposed to healed, that their requirement for milk had dropped dramatically. No need for milk, he’s looking for arrears for the milk payment. But we did get them all back and we showed, by chance I think, because Denol after all wasn’t all that effective as an antibacterial, at best 15–30 per cent were truly eradicated of the bacteria, but we showed it to be superior to cimetidine, which was the market leader.

²⁵³ Martin D, Hollanders D, May S J, Ravenscroft M, Tweedle D E, Miller J P. (1981) Difference in relapse rates of duodenal ulcer after healing with cimetidine or tripotassium dicitrato bismuthate. *Lancet* i: 7–10.

²⁵⁴ Coghlan J G, Gilligan D, Humphries H, McKenna D, Dooley C, Sweeney E, Keane C, Ó’Moráin C. (1987) *Campylobacter pylori* and recurrence of duodenal ulcers – a 12-month follow-up study. *Lancet* ii: 1109–1111.

²⁵⁵ A similar technique was used by Archie Cochrane in the Welsh Valleys, see Ness A R, Reynolds L A, Tansey E M. (eds) (2002) Population-based Research in South Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, for example, page 21 and Stewart Kilpatrick on page 37.

And, of course, we had great difficulty in convincing people about this, particularly the biomedical industry, as it was bad news. Here was a cure. As we heard share prices went up, when it was discovered that you had to take Tagamet for life, or ranitidine (the Glaxo product) you had to get on to the merry-go-round of trying to treat ulcers, whereas here a once-off treatment was a cure as opposed to a healing treatment. That certainly revolutionized my life. It opened up new areas and introduced me to some wonderful people and many of them here today are now, of course, firm friends.

I think as we consider the theme of this, what we are mostly pleased with is the fall of duodenal ulcer – people are no longer suffering from this condition. That probably is no thanks to us as medics, although I admit the hard work that we all do on behalf of our patients, but due to the improvement in the social environment. The improvement of the social environment that we now hopefully enjoy, will increase prosperity and hopefully peace. Governments will realize that the true enemy of humankind is disease and that more efforts will be put into improving our social environment and also supporting people like you who give up voluntarily your precious time to go to meetings, to spread the news, and what wonderful news we have to spread, that we can certainly cure duodenal ulcers, that they will be a thing of the past.

Pounder: Colm, do you think there was a conspiracy by the biomedical industry to damp down anything to do with *H. pylori*, or was it just that people reacted because Barry Marshall was such an evangelist? In the late 1980s I went off to talk around Australia about antisecretory drugs. I went there thinking, ‘Here I am, talking about acid, and this is Australia’s own germ’. I mentioned Barry Marshall, and there were hollow laughs from all the gastroenterologists. He was widely disliked at that stage, because he was such an evangelist for the germ.

O’Morain: No. I think that Barry Marshall’s personality led to more people listening, he’s such a strong, convincing personality. Without him I don’t think we would be where we are, and I suppose the negative aspect, of course, is he doesn’t attribute any thanks or gratitude to other people who may have helped him on the way. But still, he was very influential and very important.

There are just two aspects of the biomedical industry. One is the research arm, and the second is the marketing. Well, marketing we meet every day, there are people who come around and detail you about drugs. It was bad news for them and I think they went out of their way to suppress this information. I remember at the time, that we were organizing a meeting on *Helicobacter* in Dublin. The marketing people were told not to support this meeting, because it was bad news, and at the same time the largest number of attendees were from the research end of the pharmaceutical industry. On one side they were supporting, and on the other side trying to suppress. So I think we need to distinguish the two arms of the biomedical industry, one more friendly and the other maybe not so friendly.

Pounder: What do you think, John Wood, about the attitude of industry and the arrival of the germ?

Wood: I don't ever recall Barry Marshall coming to see us to ask for money to do large-scale trials at that time. I remember both Barry and I appearing on a BBC *Horizon* television programme on *Helicobacter*,²⁵⁶ when this accusation was levelled at the pharmaceutical industry. We took some time to appreciate that *Helicobacter pylori* was an important aetiological agent in peptic ulcer, but in some ways I think Barry's rather brash personality and the early evidence, which was somewhat anecdotal, in a way set things back, despite his major contributions. Perhaps a more scientific and balanced presentation of the facts might have prevailed earlier in terms of attracting large funding. We spent large amounts of money developing a product ranitidine bismuth citrate (Pylorid), which in the end was very effective at eradicating *Helicobacter* in combination with clarithromycin,²⁵⁷ but it has been scarcely prescribed, so despite hundreds of millions of pounds being spent by the industry to develop such drugs, these have not been embraced and taken up for whatever reasons. So I am personally not convinced that the biomedical industry set back knowledge with respect to *Helicobacter*, but that's my perception.

Pounder: I think the other thing that perturbed your involvement was the attitude of the FDA. The FDA finally accepted that eradicating *H. pylori* was a legitimate end-point, only a few years ago. Until then, if you were developing a new drug, the FDA had great control over what you did. They gave your first end-points as ulcer healing, studies had to be in ulcer patients, they had to be endoscoped, and eradicating *H. pylori* was a secondary end-point. Which meant that the people with the established drugs, the proton-pump inhibitors and the antibiotics, were not controlled by the FDA. They did one or two pivotal registration experiments, but otherwise they did lots of free-range sampling experiments. In the end they got the answer that a triple-therapy regimen seems to be the most effective.

Wood: Also low doses of Tagamet or Zantac were highly effective in maintaining patients ulcer free. Now just to take up one point that Colm Ó'Moráin was making with respect to Denol. Yes, fewer patients relapsed on Denol after cimetidine, but if you continued the cimetidine (and it was low-dose maintenance therapy), even lower numbers of patients would have relapsed. So the therapy was safe, pretty good, not so expensive, and that's why this has continued. I mean, even today not everybody is using eradication therapy and if you look at the regimens that are being used by many physicians, many of them are not supported by evidence from appropriate controlled clinical trials.

Dr Belinda Johnston: Our whole interest in *Helicobacter* was directly influenced by Gist Brocades,²⁵⁸ because we had a grant from them. We were doing physiology and

²⁵⁶ Broadcast on 16 May, 1994. Ulcer Wars. *Horizon*, BBC2. A VHS copy is held in the Wellcome Library's Medical Film and Audio Collections, 523V.

²⁵⁷ See, for example, Dixon J S, Pipkin G A, Mills J G, Wood J R. (1997) Ranitidine bismuth citrate plus clarithromycin for the eradication of *H. pylori*. *Journal of Physiology and Pharmacology* 48: 47–58.

²⁵⁸ Dr Belinda Johnston wrote: 'The pharmaceutical company who marketed Denol, a bismuth-containing drug that has activity against *H. pylori*.' E-mail to Dr Daphne Christie, 16 May 2001.

acid secretory studies, and they knew we had paired duodenal and antral biopsies and so we could look at them retrospectively. It enabled us to publish in *Gut*, in 1986, on the *Campylobacter*-like organisms (CLO) presence in both, stating that it wasn't present in intestinal metaplasia, but was in gastric metaplasia in the duodenum.²⁵⁹ It was directly because they said, 'Please look for CLO' that we were able to do the work, and when we said, 'We need more money', and they said, 'Have it, have it.'

McColl: I think there were serious problems here in implementing this new treatment, even once there was good scientific evidence that it was appropriate. And I think there were three factors that influenced this. One was clearly a professional prescribing inertia, people weren't used to thinking of ulcers being due to infection, and the profession as a whole were not ready for it, and they didn't like it. The second was that there was no pharmaceutical company promoting it. Most new treatments are promoted by pharmaceutical companies, but there was no new drug here to promote, there was no profit. Worse, there was every reason why the pharmaceutical companies in the gastrointestinal field should block this or should encourage it not to be developed, because it was going to undermine their main income. Money was being made at huge rates from cimetidine and ranitidine, and these companies were the key companies promoting gastroenterology meetings and supporting gastroenterology research. Therefore one couldn't expect them to come out and support this new treatment which might undermine their revenue. And I certainly did feel the effects of this personally. There was one BSG [British Society of Gastroenterology] meeting where we were presenting some work on *H. pylori* and its effect on physiology and gastrin. I was asked by the BSG to speak at a press conference and presented the work and then other members of the press came up to me afterwards. I was then met by one of the secretaries of the BSG at that time, and told I was not to speak to the press about this, because one of the pharmaceutical companies had complained. Now there was a sense there that pharmaceutical industries were even working through British medical societies to discourage the release of scientific knowledge that was relevant to clinical treatment. The way in which this new treatment became adopted, was not from the profession down, it was from the patients up. And it was through the press getting hold of this story and through their programmes and newspapers, that the patients demanded this new treatment. I think there is a problem when introducing a new treatment that cures a chronic condition from which the pharmaceutical companies were receiving a large income due to their drugs that controlled, rather than cured, the disease.

Dr John Atherton: Just to go back to the question of Barry Marshall. I wasn't around at the time, I am too young for that, but just to defend him a little bit. It is clear that

²⁵⁹ Dr Belinda Johnston wrote: 'The work was presented at the British Society of Gastroenterology Meeting and the abstract published in *Gut* [Johnston B J, Ali M H, Haines K, Reed P I. (1985) *Campylobacter*-like organisms (CLO) in the duodenal mucosa and the effect of ulcer treatment on their presence. *Gut* 26: A579]. The full publication was, in fact, in 1986 [Johnston B J, Reed P I, Ali M H. (1986) *Campylobacter*-like organisms in duodenal and antral endoscopic biopsies: relationship to inflammation. *Gut* 27: 1132–1137].' Letter to Dr Daphne Christie, 16 April 2002.

he did put all his energies into the early studies, in his early papers he described the potential association with cancer, which later became proven, through his reading about the longitudinal Scandinavian cohort studies. So he described all the disease associations early on. He described many of the tests that we use today.²⁶⁰ So, for example, after his initial description, I think he described it as being a urease-negative organism, but when he realized it was urease positive, the biopsy urease test was developed in Australia. [Goodwin: I think you will find that it wasn't actually. I understand that Clodna McNulty in England first described the use of a biopsy in a rapid urease test,²⁶¹ but it was then put in the gel and marketed in Australia.] I think that really sums up what he has done. He is not a typical clinical scientist, but he has had the energy to really put behind this and to really move things forward. He wasn't the first person to publish on the urea breath test, but at the time he was independently working on it and published very soon after Duncan Bell in this country and David Graham in the USA.²⁶² So I think that he must be given a lot of credit for making many of the really seminal discoveries very early on in the history of *Helicobacter pylori*-associated disease.²⁶³

Pounder: He did, of course, patent almost all of those ideas as well. He did protect his position and that might be a lesson to all of us – to motivate us to get on with discovery.

Atherton: I think that is absolutely true and sums up the man to an extent and again comments on the whole of *Helicobacter pylori* research. We have heard a bit about that and when we come on to talk about *Helicobacter pylori* genes and proteins, this is really one of the early occasions that bacterial genes and proteins have been patented for use, and this has been a problem for researchers. For example, when CagA was patented early on, for diagnostic and therapeutic vaccine use. The same for the toxin and then later on for the whole genome work, and for release of the genome sequence, which again as you know has been controlled by commercial companies largely.

Tovey: I am a little unhappy about the premise that predominates here that *Helicobacter* is the primary and only cause of duodenal ulcer. There are an increasing

²⁶⁰ See, for example, Marshall B J, Warren J R, Francis G J, Langton S T, Goodwin C S, Blincow E D. (1987) Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. *American Journal of Gastroenterology* 82: 200–210.

²⁶¹ Dent J C, McNulty C A, Uff J S, Gear M W, Wilkinson S P. (1988) *Campylobacter pylori* urease: a new serological test. *Lancet* i: 1002. *idem* (1989) Detection of *Campylobacter pylori* by the biopsy urease test: an assessment in 1445 patients. *Gut* 30: 1058–1062.

²⁶² Bell G D, Weil J, Harrison G, Morden A, Jones P H, Gant P W, Trowell J E, Yoong A K, Daneshmend T K, Logan R F. (1987) ¹⁴C-urea breath analysis, a non-invasive test for *Campylobacter pylori* in the stomach. *Lancet* i: 1367–1368. Graham D Y, Klein P D, Evans D J Jr, Evans D G, Alpert L C, Opekun A R, Boutton T W. (1987) *Campylobacter pylori* detected noninvasively by the ¹³C-urea breath test. *ibid.* i: 1174–1177. Marshall B J, Surveyor I. (1988) Carbon-14 urea breath test for the diagnosis of *Campylobacter pylori* associated gastritis. *Journal of Nuclear Medicine* 29: 11–16. See also Berger A. (2002) How does it work?: *Helicobacter pylori* breath tests. *British Medical Journal* 324: 1263.

²⁶³ See Marshall B. (2002) *Helicobacter pylori*: 20 years on. *Clinical Medicine* 2: 147–152.

number of papers available now, showing that the incidence of *H. pylori*-negative duodenal ulcer can vary from 15 up to 40 per cent, particularly in areas where the overall prevalence of *Helicobacter pylori* infection in the population is low. In those areas you are getting increasing numbers of *Helicobacter*-negative duodenal ulcer and these are not patients who are on non-steroidal anti-inflammatory drugs (NSAIDs).²⁶⁴ So I think that there is still a primary factor which needs looking into. What is the cause of duodenal gastric metaplasia for instance? And, as I have mentioned earlier on, diet perhaps provides the soil for this to happen.

Pounder: I don't think anybody would say it's absolutely the only thing, but clearly there are multiple causes.

Misiewicz: I would just like to come back to Ken McColl and his story of industrial mayhem. I accept what you say, but once dual therapy and then triple therapy became established, based on a proton-pump inhibitor with antibiotics, the pharmaceutical industry, those that made those drugs, were funding large-scale trials and without their support these trials would have never happened.

McColl: I totally agree and I am very grateful to the pharmaceutical companies for that, but the key point you make, George [Misiewicz], is that it was only when they had a vested interest in it that the money came. When the new treatment was a threat to the pharmaceutical industries' income they did not support it but in some cases actively discredited it.

Crean: Just for the record. When I was a medical student in Dublin we were concerned with measuring gastric ammonia, because Conway and Fitzgerald had, in fact, got within an inch of *Helicobacter* in the sense that they discovered gastric urease and so on.

Dr Joseph Blau: As a neurologist I feel slightly ectopic here, but in neurology we are obsessed by localization and I would be interested to know, assuming that acid and *Helicobacter* pervade the whole of the stomach, why is the ulcer localized on the lesser curvature and not on the fundus or the greater curvature? Why is it localized in one part of the duodenum and not the other three parts, or four parts?

Kirk: Having wasted 20 years trying to think about this problem, it seems to me that the two things that we have identified are acid, which has a field effect, and *Helicobacter* which has a field effect, and yet apart from the work by Oi who showed that the ulcers were just distal to a mucosal junction,²⁶⁵ we haven't discovered why ulcers are usually singular, discrete, and why they don't just become serpiginous like colitis.

²⁶⁴ See, for example, McColl K E. (2000) *Helicobacter pylori*-negative ulcer disease. *Journal of Gastroenterology* 35: 47–50. Tovey F I, Hobsley M. (1999) Is *Helicobacter pylori* the primary cause of duodenal ulceration? *Journal of Gastroenterology and Hepatology* 14: 1053–1056.

²⁶⁵ Oi M, Oshida K, Sugimura S. (1959) The location of gastric ulcers. *Gastroenterology* 36: 45–56. Oi M, Sakurai Y. (1959) The location of duodenal ulcer. *ibid.* 36: 60–64.

Hobsley: I would like to comment on two recent points that have been made. To take Jerry Kirk's point first, the ulcer in a gastric ulcer forms on the lesser curvature at the point where the non-acid producing mucosa starts, and the highest point of the subdivision between the fundal mucosa and the antral mucosa is always on the lesser curvature. That might have some bearing. I don't understand it, but that might be something that relates to why it's up there. And, of course, in the duodenum, Hugh Baron and I have already commented on the fact that duodenal ulcer is a gastric ulcer in the duodenum.

The other comment I want to take up is of Frank Tovey's about the *Helicobacter pylori*-negative ulcers. I am very familiar with the concept of a cause of disease that can be demonstrated to be present at the onset of the disease. There is one paper at least in the literature, from South America, which quite clearly documents that patients with a less than six-month history of duodenal ulcer have a much smaller incidence of *Helicobacter pylori* than those with a greater than six-month history.²⁶⁶ How that fits in with the *Helicobacter pylori* itself causing, perhaps I ought to say initiating, the ulcer is very difficult to understand. I could amplify that and strengthen that argument by reporting some of my own figures, but since I have been trying to get a sceptical medical press to publish these figures for the last five years, I think I had better forebear at the moment from saying it. I am not familiar with a cause that cannot be demonstrated at the onset of its result.

Pounder: That's the trouble, all the referees are sitting in the audience here. I think most people would accept that eradicating *H. pylori* in ulcer patients who are not taking NSAIDs, produces a long-term remission. And that, I think, is the thing that really attracted most people to *H. pylori*. When you start asking beyond that, 'How does it cause ulcers? How is it transmitted?', it gets more difficult.

Hobsley: I think you have got to say to yourself, 'Does it cause the ulcer in the first place?' You have got to be absolutely strictly logical. We have the evidence that it is an important factor in preventing the ulcer from staying healed once it has healed. As a matter of fact if you bang your shin against a metal bar, and get yourself an ulcer on the shin, it will heal quicker if you deal with the inevitable infection that ensues.

Pounder: Now Ken McColl is going to tell us really why people get ulcers, and where *H. pylori* fits in with this.

McColl: I thought I had better talk about duodenal ulcers, because they are slightly simpler. Just to be a bit descriptive, because I can remember sitting in my office in the Western Infirmary in Glasgow, where Sir Andrew Watt Kay and all the other famous people you have heard of, had sat years before, sitting there on an afternoon in 1985. I had done research in enzymology, so I knew a little bit about urease and the

²⁶⁶ Pest P, Zarate J, Varsky C, Man F, Schraier M. (1996) *Helicobacter pylori* in recently-diagnosed versus chronic duodenal ulcer. *Acta Gastroenterologica Latinoamericana* 26: 273–276.

ammonia that it produced. I had also been brought up in the very classical school of ulcers in Glasgow, so I knew all about acid. I knew that duodenal ulcer disease was really a disease of acid hypersecretion and I also knew about gastrin and that there was evidence that the acid hypersecretion in duodenal ulcer disease might well be related to gastrin. Studies had been done by John Walsh and colleagues that had shown that the ability to regulate gastrin and its release was impaired in duodenal ulcer disease and, in particular, the ability of acid in the stomach to turn off gastrin, and thus prevent over-excretion of acid, was abnormal, but the reason for that was unknown.²⁶⁷ So I had this knowledge from previous research and this concept of *H. pylori* didn't fit in with this at all.

I remember, in 1985, I had been at one of our local research meetings and somebody there stood up to talk about this bacterium in the stomach and then said it might be causing ulcers. I gave them a most awful roasting, that they didn't have an ounce of evidence, whatsoever. But I did feel a bit uncomfortable about *H. pylori*. I read up about the infection and I remember realizing that in the duodenal ulcer patients that the *H. pylori* gastritis was predominantly in the antrum, where the gastrin, of course, is produced, and that the acid secreting mucosa was healthy. And it struck me and several other people I think, Roy Pounder, John Calam, at about the same time,²⁶⁸ that the two things we now knew about duodenal ulcers, could, in fact, be part of the same aetiology. In other words the increased acid secretion and the disturbed control of gastrin release could be due to the infection. This infection in the antrum could result in excess release of gastrin, excess acid secretion and that acid secretion was damaging the duodenum, and eventually causing the duodenal ulceration. Several groups, Roy [Pounder]'s group, John Calam's, my own group, at about the same time, all did studies to see if the infection was increasing gastrin release. And, of course, it was one of these things that was so obvious, you only needed six patients and you had a significant result. Gastrin was increased by about 30 per cent in *H. pylori*-infected people. After a meal, it was up about twice normal, and more importantly, when you eradicated infection, the gastrin came back to normal very quickly.²⁶⁹ And so we knew that *H. pylori* were affecting the physiology of the stomach and, in particular, gastrin release. It was much more difficult to see whether this increased gastrin was producing excess acid secretion, and the reason for this was that most of our traditional tests of acid secretion did not measure the influence of endogenous gastrin. Finally, we stumbled on the use of gastrin-releasing peptide as an appropriate stimulus to test

²⁶⁷ Eysselein V E, Kovacs T O, Kleibeuker J H, Maxwell V, Reedy T, Walsh J H. (1992) Regulation of gastric acid secretion by gastrin in duodenal ulcer patients and healthy subjects. *Gastroenterology* 102: 1142–1148.

²⁶⁸ Levi S, Beardshall K, Haddad G, Playford R, Ghosh P, Calam J. (1989) *Campylobacter pylori* and duodenal ulcers: the gastrin link. *Lancet* i: 1167–1168. Smith J T, Pounder R E, Nwokolo C U, Lanzon-Miller S, Evans D G, Graham D Y, Evans D J. (1990) Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with *Helicobacter pylori*. *Gut* 31: 522–525.

²⁶⁹ See, for example, Calam J. (1999) *Helicobacter pylori* modulation of gastric acid. *Yale Journal of Biology and Medicine* 72: 195–202. *idem* (1995) *Helicobacter pylori*, acid and gastrin. *European Journal of Gastroenterology and Hepatology* 7: 310–317.

antral function as well as the function of the oxyntic mucosa.²⁷⁰ Following this stimulus the acid response in duodenal ulcer patients was something like six times more than normal, and if you eradicated the infection, the acid and the gastrin came down towards normal levels. So certainly, I think, in duodenal ulcer disease, we now had a unifying hypothesis. The particular pattern of gastritis that the infection was producing in duodenal ulcer patients was resulting in disruption of the physiology of the stomach. In particular, it was disrupting the acid-mediated inhibiting control of gastrin release, resulting in excess acid secretion, excess duodenal acid load, duodenal gastric metaplasia and ulceration.

Pounder: Thank you very much. Hugh, a response from the acid doctors.

Baron: I think it's worth making the distinction that you have already mentioned, between pathophysiology and pathogenesis. Although the pathophysiology of duodenal ulcer isn't fully worked out in terms of hypersecretion, the pathogenesis you have heard can be related to other factors, mainly *H. pylori*. An aged endocrinologist told me the worst thing that ever happened in diabetes mellitus was the discovery of insulin, because having solved the pathophysiology, it stopped people thinking about the pathogenesis. And the same thing happened in a sense with ulcer disease. Once powerful acid inhibitors came about, everybody was happy, except one or two people who wanted to know, 'Yes, but what is the pathogenesis of ulcer disease?' And that really only became clear for two reasons. One of which Ken McColl hinted at, our knowledge of the hormonal basis of the control of exocrine secretion. This has hardly been touched upon here, but after Graham Dockray talked about gastrin we have the whole battery of gastrointestinal hormones, the stomach being called the most important endocrine organ in the body. And there was also the work at the Hammersmith of Tony Pearse, Julia Polak and Stephen Bloom in relationship to the whole field of gastrointestinal peptides.²⁷¹ I was a hanger-on in the acid sense, but certainly about 20 years ago we could produce this perfectly good hypothesis in relationship to the failure of antral inhibition of post-prandial acid in gastrin in terms of the shortage of G cells producing somatostatin. And although effectively we had shown G-cell hyperplasia, we had shown there is an increased G-cell mass in post-prandial hypergastrinaemia and the rest of it that Ken [McColl] has described.²⁷² All we needed was factor 'X', that could explain why there were too few somatostatin cells. That 'X', of course, came later in the form of *H. pylori*. That mysterious factor turned pathophysiology into pathogenesis. Of course, not all ulcers are caused by excess acid. Not all ulcers are caused by *H. pylori*. You only have to think about

²⁷⁰ McColl K E, El-Omar E. (1995) Review article: gastrin releasing peptide and its value in assessing gastric secretory function. *Alimentary Pharmacology and Therapeutics* 9: 341–347.

²⁷¹ See, for example, Thompson J C. (ed.) (1975) *Gastrointestinal Hormones. A symposium*. Austin, London: University of Texas Press, 155–168, 257–268.

²⁷² Royston C M, Polak J, Bloom S R, Cooke W M, Russell R C, Pearse A G, Spencer J, Welbourn R B, Baron J H. (1978) G cell population of the gastric antrum, plasma gastrin, and gastric acid secretion in patients with and without duodenal ulcer. *Gut* 19: 689–698.

Zollinger–Ellison syndrome – if you pour enough acid on to a duodenum it will turn into gastric metaplasia, which can ulcerate even if there's no *H. pylori* and so on.

The second thing I wanted to talk about is again this paradigm shift. When the first work on *H. pylori* came out, it became glaringly obvious to various people around the world that this was the mysterious 'X' factor, but as has been said, this did not convince the two vital groups. It certainly should have interested the pharmaceutical industry, but it is no use blaming them. It certainly didn't interest the members or officers of the AGA or the BSG, both of which I knew. There was no enthusiasm. Although I was on the programme committee of the BSG for many years, I was even President of the BSG, but in no way could I interest anybody there that any of the educational half days or whole days should have any programme content on *Helicobacter pylori*. And when it came to it, as has been said, the key influence didn't come from the doctors, it didn't come from the industry, it came from prodding from politicians. And this was Barry Marshall writing to Senator Kefauver (I believe) asking why the USA spent thousands of millions of dollars on acid inhibitors, when he could cure any ulcer for \$5. And that led, of course, to the famous NIH Consensus Conference that was fascinating.²⁷³ I and one or two others here were there. Almost all the acid doctors came along and said, '*H. Pylori* was all nonsense'. But a fairly impartial panel of people who were not primarily ulcerologists came out with the simple rule that has guided us all since then, that all patients with ulcers with *Helicobacter pylori* should have the *Helicobacter pylori* eradicated. That caused a total shift. I remember talking to all the pharmaceutical companies before, during and immediately after that meeting, and everybody was 'about turn, off we go'.

Booth: Can I just make a correction there? Hugh's covered a huge amount of territory in that brief talk, but I would just like to point out that the people who discovered the hormones of the small intestine and the large intestine were not Pearse and his followers at the Hammersmith, but Victor Mutt and Jorpes in Stockholm, and they should be given the credit for that.²⁷⁴

Hobsley: I fully take the elegance of pathophysiological mechanisms about gastrin and the active chronic gastritis, which I believe certainly in my series [of patients], is very closely, 100 per cent associated with the presence of *Helicobacter pylori*, but it's not 100 per cent associated with duodenal ulcer. I am fully convinced that there is something about the chronicity of the ulcer that is very important. There is just one other factor that I am a little bit worried about. If the increased gastrin, and failure to cut that off – that is, to cut off the gastric secretion – is the important factor, it can't be associated with an increased parietal-cell mass, because we know that comparing duodenal ulcer patients with *Helicobacter pylori*, and duodenal ulcer patients without

²⁷³ NIH Consensus Conference. (1994) *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Journal of the American Medical Association* 272: 65–69.

²⁷⁴ Mutt V, Jorpes E. (1971) Hormonal polypeptides of the upper intestine. *Biochemical Journal* 125: 57P–58P. op. cit. note 271.

Helicobacter pylori, that the ones without *Helicobacter pylori* secrete more acid by maximal gastric secretion tests.²⁷⁵ They can't secrete any more acid, whether they have got gastrin there or not. That is the 100 per cent mark. So it can't be the excess parietal-cell mass, it can only be that the gastrin secretion results in an increased output during the 24 hours just as the Zollinger–Ellison syndrome is concerned with. Has that been measured I wonder? And is basal secretion a higher fraction of maximal secretion as it is in the Zollinger–Ellison syndrome?

Tyrrell: Two short points. One is that I collaborated with people working in the pharmaceutical industry and that one of the things that I was taught was that nobody like the Medical Research Council pays for their research. What pays for their research is the last successful drug that they made and marketed. So we inevitably have a stressed, somewhat polarized, situation, within the pharmaceutical industry as to how they are going to use the products of the scientific group. I agree with what other people have said, but research workers in industry seem to be very like the academic types when you talk to them and what they want to do. But the people who market are different and I suppose they have to be different, because they have got a different job to do. And so I understand the problem, but I think it is difficult to try to attach blame to people for the way a system works out at times.

Jones: Yes. I wanted just to think a bit more about the diffusion of innovation and advance in technology that we have been hearing about over the last 20 or 30 years. From my primary care point of view, gastroenterology is an unusual case, and I include in this both the H2 blockers, the use of endoscopy, proton-pump inhibitors, and dealing with *Helicobacter*. It's unusual in the sense that in almost all other significant conditions we under-treat, we under-prescribe statins, we under-prescribe aspirin, we under-diagnose hypertension, and we under-treat asthma. In most of the gastrointestinal disorders behaviour is characterized by over-use and by attempts to reduce excess or inappropriate prescribing of H2 blockers and the appropriate prescribing of proton-pump inhibitors. I don't know what the reasons for this are. Some of the comments about the role of the industry, the role of research, and the role of the public, are clearly important, but in some way some of these innovations have got into the primary care prescribing and management much quicker, ahead of the evidence almost. And I would be interested in comments about that.

Pounder: The big difference about antisecretory drugs is that most patients, by and large, feel better when they are taking them. Whereas with statins and things like that, it's the doctor who cajoles the patient to take the treatment. Treating hypertension, patients have a strong negative feedback due to a very large number of adverse symptoms. Although I have an enormous respect for the marketeers of the antisecretory drugs, I think these drugs largely sold themselves, because people felt better.

²⁷⁵ Chandrakumaran K, Vaira D, Hobsley M. (1994) Duodenal ulcer, *Helicobacter pylori* and gastric secretion. *Gut* 35: 1033–1036.

Wood: These conditions are (a) very, very, very common, and (b) highly symptomatic. People are not aware that they have got hypercholesterolaemia or raised blood pressure, so they don't badger their doctor for more treatments. They are also quite effective in dietary indiscretion, hangovers and a whole range of things, and as these medicines have now moved over the counter, people actually prescribe them for themselves, for a whole variety of conditions. It's not over-prescribing by physicians *per se*, although obviously these drugs have been used very widely and in some patients inappropriately. But people are now purchasing these medicines, to re-treat themselves.

Hunter: I wonder if I could make one point about this debate on pharmaceutical companies and profit. It was made by Sir Derrick Dunlop. He compared the record of drug discovery of the Soviet Union with that of the Western world and the Soviet Union actually failed to discover one single drug. If I may be allowed to use irony, I might say, the trouble about the wicked pharmaceutical capitalists is that they are guilty of making sick people better.

Pounder: I have a slide of a Russian treatment for ulcer disease. It was called Bukovina-One. Bukovina-One was a mineral water, which I described as an H₂O ulcer antagonist.

Northfield: Can I come back on the mechanism of action of *H. pylori*? I think, apart from the obviously very important effect on acid secretion, that there's also a mucosal defence aspect of this, affecting gastric hydrophobicity, mucosal bicarbonate barrier and mucosal thickness. I have been involved in gastric hydrophobicity and my interest in that dates from hearing a lecture in the USA, I think by Brian Hills, in which he and Len Lichtenberger were describing mucosal hydrophobicity in the dog as a part of physiology. They argued that the dog's stomach needed some protection against all the acid that was in the stomach, and they had done some measurements showing that it had a high hydrophobicity, that is to say the mucosa was repelling fluids, including acid, and they attributed it to phospholipids, surface-active phospholipids.²⁷⁶ Being interested in bile, I thought, 'Well, phospholipids sounds like bile to me, so I will get involved in this', and that is how I got interested in *H. pylori*. The first stage was to show that hydrophobicity was reduced in patients with peptic ulcers. Our second move was to show that it was reduced in patients who had *Helicobacter pylori* infections. The third was to show that eradication in *H. pylori* infection raised hydrophobicity again to normal levels. So I think there is a mucosal defence aspect to this problem.

Tyrrell: A different topic. Infections may be involved in quite a lot of chronic diseases. I am reminded of the fact that poliomyelitis was once thought of as a paralysis, a neurological problem. Then it was shown to be due to a virus infection and thereafter many people thought of the disease in terms of straight infection, immunity, etc. But that didn't invalidate the fact that it had been shown by family studies that there was

²⁷⁶ Hills B A, Lichtenberger L M. (1985) Gastric mucosal barrier: hydrophobicity of stretched stomach lining. *American Journal of Physiology* 248: G643–G647.

a genetic component, that there was a physiological component, paralysis occurred in exercised limbs, and a traumatic effect – if people had injections, that that was the side that got the lesion. Having shown that there was this relationship between infection and the other things, the next stage was to work out the mechanisms, how did they interrelate? I can't help thinking that there's something like the same operation going on now. We knew that you mustn't give live polio vaccine to children who have just been given whooping cough vaccine, but we don't still know how it is that the whooping cough vaccine makes the child more vulnerable to paralysis from the virus infection. There are going to be no general answers, but in principle you move from showing that something is a relevant factor, to showing how it works and possibly, if need be, how you can intervene.

Pounder: John Atherton. Tell us your position with *Helicobacter pylori*, as a younger witness.

Atherton: I first became interested in *Helicobacter pylori* in 1991 when I went up as a research fellow to Nottingham looking at *Helicobacter pylori* treatment. I spent two years looking at dual therapy for eradication of *Helicobacter pylori* and was rescued by Bazzoli's description of the low-dose triple therapy regimen which are in common use today.²⁷⁷ While I was in Nottingham what struck me was a question that we've touched on several times, which is that a lot of people are infected with *Helicobacter pylori*, but very few get duodenal or gastric ulcers, or gastric cancer (which we haven't talked too much about this session – this meeting hasn't really been about that). I was struck as I was treating these patients in my treatment trials, that I was treating many people who were infected, but who were entirely asymptomatic. This was an exciting time for microbiology research, and I looked avidly at the microbiologists, as a gastroenterologist, thinking that that was where the advances were coming from. In 1988, again in a pharmaceutical company environment, the cytotoxic activity of *Helicobacter pylori* was described by Leunk.²⁷⁸ Later, in the USA, Tim Cover and Martin Blaser purified the cytotoxin and at roughly the same time, again in the USA, another protein called CagA, which seemed to be non-toxigenic, was shown to be associated with toxin production.²⁷⁹ Then Jean Crabtree in the UK provided the first evidence that an antibody response to the CagA protein seemed to be present in most people with peptic ulcer disease.²⁸⁰

²⁷⁷ Jaup B H, Norrby A. (1995) Low dose short-term triple therapy for cure of *Helicobacter pylori* infection and healing of peptic ulcers. *American Journal of Gastroenterology* **90**: 943–945. Bazzoli F. (1999) My approach to *Helicobacter pylori* eradication. *European Journal of Gastroenterology and Hepatology* **11**: S37–S41.

²⁷⁸ Leunk R D, Johnson P T, David B C, Kraft W G, Morgan D R. (1988) Cytotoxic activity in broth-culture filtrates of *Campylobacter pylori*. *Journal of Medical Microbiology* **26**: 93–99.

²⁷⁹ Cover T L, Dooley C P, Blaser M J. (1990) Characterization of and human serologic response to proteins in *Helicobacter pylori* broth culture supernatants with vacuolizing cytotoxin activity. *Infection and Immunity* **58**: 603–610.

²⁸⁰ Crabtree J E, Taylor J D, Wyatt J I, Heatley R V, Shallcross T M, Tompkins D S, Rathbone B J. (1991) Mucosal IgA recognition of *Helicobacter pylori* 120 kDa protein, peptic ulceration, and gastric pathology. *Lancet* **338**: 332–335.

I was excited by this work and went out to the USA in 1993 to work in Martin Blaser's laboratory. I remember the very exciting race to clone and sequence the vacuolating cytotoxic gene and Tim Cover's laboratory working towards that end in the first year that I was there. Then, as in all these things, it led to some dead ends. It seemed to look like an IgA protease, but had no IgA protease activity, and subsequently the work by Tombola and co-workers in 1999, showed that it was, in fact, a pore-forming toxin.²⁸¹ But I became interested in why when this toxin seemed to be present in all strains, only some of them were toxigenic, and we described mosaicism in this gene and genetic variation, and showed how this was important for the differences between *Helicobacter pylori* strains.²⁸² This came at an opportune time, because at this time there was an enormous interest in variation between strains of bacterial species and it was shown that my bacteria weren't just undergoing clonal expansion, but were in fact swapping DNA, recombining, in a way analogous to our human sexual reproduction. At the same time CagA was becoming better understood, and we now know that some strains of *Helicobacter pylori*, the more pathogenic strains, export this CagA and it's actually injected into host cells, where it interferes with host-cell signalling as first published by Stanley Falkow's group in 1999.²⁸³ So I was excited to be involved with research in bacterial pathogenicity, but all the time we had been conscious that bacterial pathogenicity is only one reason why some people get disease and others don't.

We talked about the very important contribution of the environment earlier on this morning, and another really seminal paper in this field has come with the publication in *Nature* from Emad El-Omar, originally from Ken McColl's group, who has shown that not only are there differences in *Helicobacter pylori* genes, but there are polymorphic differences in human genes that control interleukin-1 expression.²⁸⁴ Interleukin-1 is thought to affect acid production levels in the stomach and genetic differences between people in the level of interleukin-1 expression may be one reason why some people develop ulcers and other people develop cancer. I don't know, Ken, if you would like to comment any further on that work?

McColl: I support what you have said, John. The key question now is why some people get ulcers, and others don't. Why is it that the same infection can produce

²⁸¹ Tombola F, Carlesso C, Szabo I, de Bernard M, Reyrat J M, Telford J L, Rappuoli R, Montecucco C, Papini E, Zoratti M. (1999) *Helicobacter pylori* vacuolating toxin forms anion-selective channels in planar lipid bilayers: possible implications for the mechanism of cellular vacuolation. *Biophysical Journal* 76: 1401–1409.

²⁸² Atherton J C, Peek R M, Tham K T, Cover T L, Blaser M J. (1997) Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of *Helicobacter pylori*. *Gastroenterology* 112: 92–99.

²⁸³ Segal E D, Cha J, Lo J, Falkow S, Tompkins L S. (1999) Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. *Proceedings of the National Academy of Sciences of the USA* 96: 14559–14564.

²⁸⁴ El-Omar E M, Carrington M, Chow W H, McColl K E, Bream J H, Young H A, Herrera J, Lissowska J, Yuan C C, Rothman N, Lanyon G, Martin M, Fraumeni J F, Rabkin C S. (2000) The role of interleukin-1 polymorphisms in the pathogenesis of gastric cancer. *Nature* 404: 398–402.

duodenal ulcers in some people but gastric cancer in others.²⁸⁵ As discussed earlier, dietary factors may be important. Another factor seems to be the virulence of the organism, as shown by your own work. A third factor is the genetically determined host response to the infection, as shown by Professor El-Omar.²⁸⁶ So the pathogenesis of ulcer disease is very complex. It is due to interactions between host factors, environmental factors such as smoking and diet, and the bacterium. The fortunate thing is that if you just remove the infection, you cure the disease. It's the essential cofactor in the equation.

Pounder: This germ, or similar spiral organisms, is highly conserved through the animal kingdom. Every animal seems to have its own spiral organism. One imagines that 1000 years ago, we all had spiral organisms, and now fewer and fewer have got them. Do you believe that the tolerance of this chronic infection has a benefit? Who can tell me the benefit of having *H. pylori* infection? It would need to be a survival benefit. Something that's going to make you reproduce more successfully.

McColl: I don't at the moment know of any definite benefit. The only slight benefit that has been suggested by some people is that the infection may protect from reflux disease and associated cancer.

Pounder: Well, that's not going to make us survive longer to breed successfully, is it?

McColl: No, that's right.

Pounder: John, have you got some evidence for benefit? I know you have thought about it.

Atherton: No. I haven't got any evidence for benefit at all. I think if you are going to look for benefit, then maybe children are the place to look. We think *H. pylori* is acquired as a childhood disease, and it may be that if there is some sort of benefit, that's where it is, but I have no evidence for benefit whatsoever. Unlike Professor McColl, I am becoming more convinced of the evidence that *Helicobacter pylori* is protective against oesophageal disease.

Pounder: It's like an antisecretory drug, isn't it? A damaged stomach doesn't secrete so much acid. Once you get the stomach healthy, it makes more acid. We are all getting fatter and we get reflux.

Atherton: Absolutely, I think that in retrospect it's easy to see the mechanism for this and there are now very good population studies correlating, for example, serological

²⁸⁵ See also Forman D, Newell D G, Fullerton F, Yarnell J W G, Stacey A R, Wald N, Sitas F. (1991) Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *British Medical Journal* **302**: 1302–1305. Ness A R, Reynolds L A, Tansey E M. (eds) (2002) op. cit. note 255, for example page 81.

²⁸⁶ op. cit. note 284.

markers of atrophy like pepsinogen ratios or *Helicobacter pylori* infection and screening large populations with gastroscopy.²⁸⁷ *H. pylori* infection, but even more so pepsinogen ratios, are big negative risk factors for the development of reflux oesophagitis. As you are aware there are several lines of evidence that suggest this, none of which are proven at the moment, but to me this is one of the most compelling.

Pounder: Now, here is Robert Logan, a chap whose life has been dominated for the last 15 years with this germ and ulcer disease.

Logan: I would like to start by making a few points if I may. George Misiewicz started by talking about three bits of luck. I also had three bits of very good advice, the first of which was that I ought, if I wanted to do research, to do it with George Misiewicz and Hugh Baron. The second was some advice from my brother which was, and this was in about 1986, that I ought to go and work on this new germ called *Campylobacter* and think about doing some breath testing on it. Well, at that stage as a second-year registrar, I went off and looked at *Campylobacter*: couldn't see what it had to do with breath testing and didn't know quite what he was going on about. When I eventually discovered what he was going on about, the third bit of advice I got was from my father, who said that if you are going to do any research, you want to make sure that you have got a team working together, and the way to get people to work together is to sit down round a table and share the results. It is also interesting to note that at the time when I told him about working with Denol and looking at this germ, he said, 'Well, that's what I did when I worked with Sir Francis Avery Jones at the Central Middlesex Hospital'. Unbeknown to me he had been approached by Denol, or rather the people that made bismuth, to do research and look at this drug and see how it worked on ulcer disease. And he turned it down for the same reason as Sir Richard Doll decided to look at bland diet, and that's because he believed in social medicine and he wasn't going to accept any 'filthy lucre' from the drug companies! I have to say, of course, that I wasn't quite so principled.

In fact, when it came to the three bits of good luck, the first one was when I went to St Mary's I wanted to be a chest physician, having worked with Professor Anne Tattersfield in Nottingham, to where I eventually returned, and I was convinced that chest medicine was the way forward. Unfortunately they couldn't accommodate me and they said, 'Do you mind learning endoscopy?' And I said, 'Well, it must be easier than bronchoscopy, there's only one way to go and that's forward.' So I ended up doing gastroenterology. And the second bit of luck was when it came to doing research and I had thought of these ideas on *Helicobacter*. In fact Hugh and I worked up a proposal on *Helicobacter* to try to establish that it absolutely proved duodenal ulcer disease. I can remember to this day going along to see George [Misiewicz] with this proposal and handing it to him and saying, 'This is what I want to do, please read it'. And he said, 'Yes, well, I am not sure there's much in this. Read this proposal', and it

²⁸⁷ Koike T, Ohara S, Sekine H, Iijima K, Kato K, Shimosegawa T, Toyota T. (1999) *Helicobacter pylori* infection inhibits reflux oesophagitis by reducing atrophic gastritis. *American Journal of Gastroenterology* 94: 3468–3472.

was a proposal to look at reflux oesophagitis. This was about two or three months before the very first international meeting on *Helicobacter*, which was to be held in Bordeaux. Hugh and I were going off to this meeting, and George had decided to stay at home. At the last minute he changed his mind and there was a big hoo-haa about trying to get him on the flight and find a hotel room. George came along, but didn't go to many of the sessions. However, he looked at all the posters, and as we came back he said to me, 'Robert, I think I want that proposal again, I think we need to have a meeting to sit down and discuss it'. And we worked up this proposal and actually the Wellcome Trust turned it down. But we had the good fortune to meet John Wood, and at this time Glaxo had no real interest in *Helicobacter*, but John Wood had the foresight to realize that this was probably a study that was worth funding; and he funded it, to a far greater extent than he needed, because the third bit of luck that we had was the decision to use a stable isotope.

While I did a lot of work on the urea breath test and we had the choice of either using the radioactive isotope, which my brother had been referring to, or using the much more expensive stable isotope, Hugh insisted that we should use the stable isotope. I have to say with hindsight, that was one of the best bits of advice, or luck, or whatever, that we had, because I am sure the outcome would have been very different if we had been lumbered with having to do all our tests using a radioactive isotope.

I think it is also useful to comment on the impact that this test has had on our practice. When I was learning endoscopy, we had patients who would come in to day surgery. This wasn't an endoscopy unit, it was day surgery. They would come in for a surgical procedure, they would get on the examination couch, they would be given sedation, and we would endoscope them, and when we had finished the endoscopy, we would put the endoscope in the bucket, wash it with soapy water, brush it through, rinse down with distilled water and put it into the next patient. The concept that we could have been transmitting something just didn't occur to us. And most of the patients we were endoscoping were patients that we had seen in the clinic whom we knew had ulcer disease, who were taking H₂ antagonists, who continued to smoke, and had persistent symptoms. And we wanted to know whether they had persistent ulceration. We didn't see any reflux oesophagitis, it was all chronic ulcer disease. In fact, at that time, people alluded to the amount of scepticism that there was regarding the role of *Helicobacter* in duodenal ulcer disease and particularly to the studies that had come out from Australia. That was the reason that we had gone back to work out what were the precise studies that we could do to really prove to sceptics that *H. pylori* was the real cause of ulcer disease.

By developing the breath test, and showing what effect it had on bismuth or what effect bismuth had on the organism, it immediately became apparent that you could suppress the organism to undetectable levels by this sensitive test and yet ulcers would recur after stopping the treatment, but that they could recur any period from three or four weeks to possibly five or six months, but before they recurred they always had *Helicobacter* there, as shown by the positive breath tests.

And, by showing that the bismuth only had a very transient effect, we went on to realize that we had to use it with antibiotics. We saw the paper from Dublin,²⁸⁸ looking at bismuth and metronidazole, and so we knew we needed two antibiotics. We sat down, and just like they did, worked out the dose of cimetidine, we were around a table and said, ‘Well, we take a week of this and we take these antibiotics like that, that will probably work.’ I thought the real test of this regimen would be to not use any H2 antagonists to heal the ulcers. If we thought the germ was causing the ulcer, what we wanted to do was to just treat it with our antibiotic regimen and bismuth, and see that it healed. Hugh thought this was an excellent idea, but, of course, George was not quite so keen and there was a lot of, ‘Well, if you think this is going to work, well OK we will see what happens’. So we started recruiting patients.

The design of the study was they had their ulcer diagnosed at endoscopy, they got their antibiotics, and as soon as we had documented that they had got a negative breath test, which was in two or three days of finishing a one-week regime, we would re-endoscope them. So some of these patients were getting re-endoscoped nine days later. And I can remember the excitement when I put the scope down, to see that these patients’ ulcers had completely gone and what was more, not only had they completely gone, but their duodenum, having previously been scarred and deformed, had returned to practically normal. I went back with weekly reports to George to say, ‘Well, this is the seventh one, George’, of course, it was an uncontrolled trial at that stage, but we just wanted to document that it actually worked before doing a randomized study, which came later. But we had seven in a row and they all healed. It was only with the ninth one when the patient didn’t heal that we, in fact, documented that he didn’t heal because he had still got a resistant organism. I think it was then that we realized that we were really on to something and that this was going to change everything and of course the rest is history. We have seen what’s happened since.

People talk about the problems of trying to convince different audiences of what was going on and Hugh Baron referred to the BSG committee and the AGA committee, about reluctance to take on these ideas. I actually take it a stage further. I don’t think it was anything to do with committees themselves. It was the people who were on the committees and who they were representing. I think when the Americans got a hint of what might have been happening and how this might affect their practice, there was understandable reluctance to say, right we need to be eradicating *Helicobacter*, possibly reducing our annual income in doing so. If one had to identify a key paper that made them say, ‘No we don’t have any alternative’, it was Hentschel’s paper that was published in an American journal, of course, *The New England Journal of Medicine*, in 1993, showing the powerful effect of antibiotics on the prevention of ulcer relapse.²⁸⁹

²⁸⁸ See O’Riordan T, Mathai E, Tobin E, McKenna D, Keane C, Sweeney E, Ó’Moráin C. (1990) Adjuvant antibiotic therapy in duodenal ulcers treated with colloidal bismuth subcitrate. *Gut* 31: 999–1002.

²⁸⁹ Hentschel E, Brandstätter G, Dragosics B, Hirschl A M, Nemeč H, Schütze K, Taufer K, Würzler H. (1993) Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *New England Journal of Medicine* 328: 308–312.

You also asked me to talk about diagnosis and I think one of the problems that we have had is initially with the problems of diagnosis and recognizing the organism. Certainly when I was working on developing the breath test and proving that it was probably the best test that we had at the time, one problem was apparently false-positive or false-negative results, and it was only because we had taken lots of biopsies from lots of parts of the stomach that we were able to go back and look at this material retrospectively when we realized that these weren't in fact false-positive or false-negative results, but it was due to sampling error. I think we are in a similar position now when we look at the near patient tests that a lot of our practice has been confused by using near patient tests. At the time these were thought to be quite accurate, but with hindsight have proven to be less accurate. Although of course in future this may all change with the new stool antigen tests, which I think will change how we investigate our patients.²⁹⁰

Pounder: Thank you very much indeed. Jerry Kirk and I first met at the Central Middlesex, when he was at the Central and Willesden General. I then ended up at the Royal Free, and Jerry was already ensconced up in Hampstead. Jerry, tell us a few words about your involvement in ulcer disease.

Kirk: I shan't take long, because I know the time is up and I have to say to you that surgeons got into peptic ulcer treatment reluctantly, and I hope we weren't reluctant to get out of it in view of all the damage we have done. Probably you know that the first time surgeons operated on peptic ulcers was unknowingly, because they were, in fact, treating the mechanical problem of pyloric stenosis, without realizing it was the result of duodenal ulcer. And when Rydygier in Chelmno in Poland first did a therapeutic operation of gastrectomy for benign gastric ulcer, he was howled down when the report was published.²⁹¹ An abstract of the article was published. The abstract editor wrote, 'First gastrectomy for benign gastric ulcer' and added in his own words, 'And I hope the last'.

I have never had much time for Moynihan, to be honest with you. I hardly dare say that in front of such an audience, but I think he was the sort of chap who thought that everything he said ought to be carved into stone for posterity. At my hometown in Nottingham in 1926 Hans Finsterer came over from Vienna and said that gastroenterostomy had a high recurrence rate. Moynihan was doing gastroenterostomy on the assumption that everyone had taken, that it seemed to make people with pyloric stenosis better. Then they discovered that pyloric stenosis was

²⁹⁰ See Vaira D, Vakil N, Menegatti M, van't Hoff B, Ricci C, Gatta L, Gasbarrini G, Quina M, Pajares Garcia J M, van Der Ende A, van Der Hulst R, Anti M, Duarte C, Gisbert J P, Miglioli M, Tytgat G. (2002) The stool antigen test for detection of *Helicobacter pylori* after eradication therapy. *Annals of Internal Medicine* 136: 280–287.

²⁹¹ Rydygier L. (1881) Pierwszy przypadek wycięcia odzwiernika celem usunięcia zwężenia wskutek wrzodu. *Wyzdrowienie Przegląd Lekarski* 20: 263–267. *idem* (1906) Kilka uwag o wycinaniu żołądka w 25 rocznicę pierwszego mego wycięcia odzwiernika. *ibid.* 44: 234–236. See also Sablinski T, Tilney N L. (1991) Ludwik Rydygier and the first gastrectomy for peptic ulcer. *Surgery, Gynecology and Obstetrics* 172: 493–496.

caused by duodenal ulcer, and they said, ‘Well, it makes them so much better, perhaps we ought to do it for duodenal ulcer without pyloric stenosis.’ And it got so popular that some cynics said, ‘You only have to walk past some hospitals and belch loudly and you get taken in to have a gastroenterostomy performed on you’. And, ‘It’s a pity that God didn’t fit us up with a gastroenterostomy to save us from having one later in life.’

But Finsterer showed that there was a high incidence of recurrent ulcer after gastroenterostomy and he therefore advocated partial gastrectomy.²⁹² In my younger days I thought Moynihan was very arrogant in saying, ‘Typical Germanic attitude, making something difficult out of something that’s easy. I only get 2 per cent recurrence’. And, of course, my own chief Norman Tanner found there was a 45 per cent recurrence after gastroenterostomy, but he didn’t say, and nobody said, that not all that 45 per cent required further surgery. Some of them got better on their own, or could be managed with whatever medical treatment was available.

I think you mentioned earlier, Roy, that surgeons went mad to do something to prevent all recurrent ulcers, instead of using the simplest treatment and waiting to see how the patient fared. Fifty per cent would have remained free of recurrence if we had done a gastroenterostomy alone on them. If they had intractable recurrence we could treat the minority who required it and leave the rest of them alone. All you physicians at least can stop giving patients the tablets, but you cannot undo surgical work. I remember Sir Charles Illingworth at some meeting saying, ‘Aren’t we lucky to be gastric surgeons; we can talk about “my operation for duodenal ulcer”, we can talk of anastomosis of the proximal jejunal loop to the lesser curve, or the other way – and if we have exhausted all the ways of doing the operations we can talk about “my revision operation for the gastric cripples”’. Well, he didn’t say it, but he could have said, ‘The gastric cripples we have produced’. So I don’t think that our part in peptic ulcer treatment has been very honourable. I think we should now leave it to you physicians.

Pounder: I once had a slide that said, ‘I would rather be treated for my duodenal ulcer by a house physician writing his first prescription, than a surgeon doing any of his first 50 vagotomies’. Ulcer surgery was gradually revised and revised, and in the end became very safe. Then we found the first antisecretory drugs. Then a range of antisecretory drugs that were safe, effective, but weren’t curing people. For some people, for many people, we now have the eradication of *Helicobacter pylori*, a cure. This is an inspiring story. Successive hurdles have been jumped, and things are getting better and better. Even when we thought that we had a clever solution, there was something even better around the corner. I think that is a good message for all of us, and for our patients, and for the future. Thank you all very much for contributing, joining in – it’s been a very enjoyable day.

²⁹² See Finsterer H. (1950) *My Experience with the Surgical Treatment of Gastric and Duodenal Ulcers*. Knoxville: Acuff Clinic Bulletin Supplement.

Booth: I think that this has been an extraordinarily successful day. There are copies of other Witness Seminar publications outside and I might commend to you the previously published volumes which I am sure all your libraries really should have in their collection and they are available from the Wellcome Trust, if you would like to have them.²⁹³ I think also the audience here shows the importance of this topic which has been one of the major changed concepts of human disease during the twentieth century, so affected by the fact that we have had one Nobel Laureate, three Fellows of the Royal Society, a huge number of Professors and we should have had a Noble Lord, but he sadly has been detained by legislative business, which he's now responsible for. So, may I thank you all for coming. I am sure you would also like to thank Tilli Tansey's staff, Lois Reynolds, Daphne Christie and Wendy Kutner, but we would like to thank them and thank Tilli Tansey very much indeed for including this very exciting topic in her programme of seminars. And finally to thank the Chairman who really chose you all and helped in setting the whole thing up. Roy, we are very grateful to you too. So thank you very much indeed.

²⁹³ Details of the series can be found at www.ucl.ac.uk/histmed. See also page v–vii.

BIOGRAPHICAL NOTES

Professor Ian Aird

ChM FRCSed HonFACS (1905–62) was Professor of Surgery, University of London from 1946, and Director of the Surgical Unit, London Postgraduate Medical School, Hammersmith Hospital, London. See Aird I. (1961) *The Making of a Surgeon*. London: Butterworths. Robinson R H O B, Le Fanu W R. (1970) Aird, Ian. *Lives of the Fellows of the Royal College of Surgeons of England, 1952–1964*. Edinburgh, London: E & S Livingstone, 5–6.

Dr Richard John Asher

FRCP (1912–69) was appointed physician to the Central Middlesex Hospital in 1942, becoming consultant physician in 1949. He held this post until 1963. His main interest was in the physical basis of mental illness. See Fox T, Wolstenholme G. (1982) Richard John Asher. *Munk's Roll* 6: 16–17.

Dr John Atherton

FRCP (b. 1960) studied medicine at Cambridge and Oxford Universities and graduated in 1986. He started research into *H. pylori* treatment with Dr Robin Spiller and Professor Christopher Hawkey in Nottingham, with Dr Timothy Cover and Professor Martin Blaser in Nashville, USA, and in 1996, returned to Nottingham. He is now Professor in Gastroenterology and MRC Senior Clinical Fellow.

Sir Francis Avery Jones

Kt CBE FRCP (1910–98) was Consulting Physician, Gastroenterological Department, Central Middlesex Hospital, London (1940–74), Consulting Gastroenterologist, St Mark's Hospital, (1948–78), and Honorary Consulting Physician, St Bartholomew's Hospital, London, from 1978. See Anonymous. Sir Francis Avery Jones. *The Times*, 13 May 1998, 21. op. cit. note 8.

Dr (Jeremy) Hugh Baron

FRCP FRCPG FRCS (b. 1931) was Consultant Physician at the Prince of Wales and St Ann's Hospital, Tottenham (1968–71), Senior Lecturer and Honorary Consultant, Departments of Surgery and Medicine, Royal Postgraduate Medical School and Hammersmith Hospital, London (1968–96), Consultant Physician and Gastroenterologist at St Charles Hospital, London (1971–94), Consultant

Physician and Gastroenterologist at St Mary's Hospital, London, and Honorary Clinical Senior Lecturer at St Mary's Hospital Medical School, Imperial College of Science, Technology and Medicine, London, from 1988 to 1996. Since his retirement in 1996 he has been Honorary Professorial Lecturer in the Gastroenterology Division of the Department of Medicine at Mount Sinai School of Medicine, New York. His main interests include the history of gastric secretion, peptic ulcer and *H. pylori*. Published works include *Clinical Tests of Gastric Secretion: History, methodology and interpretation* (London: Macmillan, 1978), *Cimetidine in the 80s* (Edinburgh: Churchill Livingstone, 1981), *Vagotomy in Modern Surgical Practice* (London: Butterworths, 1982) and *History of the British Society of Gastroenterology, 1937–1987* (London: BMA, 1987).

Professor Sir James Black

Kt OM FRCP FRS (b. 1924) was Professor and Head of the Department of Pharmacology, University College London, from 1973 to 1977, Director of Therapeutic Research at Wellcome Research Laboratories, from 1978 to 1984, Professor of Analytical Pharmacology at King's College Hospital Medical School, London, from 1984 to 1993, later Emeritus. He has been Chancellor of Dundee University since 1992. He shared the 1988 Nobel Prize for Physiology or Medicine for 'discoveries of important principles for drug treatment' with George Hitchings (1905–98) and Gertrude Elion (1918–99).

Dr Joseph N Blau

FRCP FRCPATH (b. 1928) trained in neurology at the London and Maida Vale Hospitals, and then in immunology at the Massachusetts General Hospital, Boston, USA. As a consultant neurologist at the National Hospitals, Queen Square and Maida Vale, he continued research at Guy's Hospital Pathology Department working on the thymus, and as consultant neurologist to the National Throat, Nose and Ear Hospital, London, and at Northwick Park Hospital did clinical research on migraine and other headaches. He is Honorary Medical Director at the City of London Migraine Clinic.

Sir Christopher Booth

Kt FRCP (b. 1924) trained as a gastroenterologist and was the first Convenor of the Wellcome Trust's History of Twentieth Century Medicine Group, from 1990 to 1996, and Harveian Librarian at the Royal College of Physicians from 1989 to 1997. He was Professor of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, from 1966 to 1977 and Director of the Medical Research Council's Clinical Research Centre, Northwick Park Hospital, Harrow, from 1978 to 1988.

Professor Wilfred Card

FRCP FRCPE FRCPG (1908–85) was Physician to St Thomas' Hospital, London (1939–48), Reader in Medicine, Edinburgh University (1948–66) and Professor of Medicine in Mathematics and Computing, University of Glasgow (1966–74). See Strong J. (1989) Wilfred Card. *Munk's Roll* 8: 76–78.

Mr Roger Celestin

FRCS (b. 1925) graduated in 1951 from University College Hospital Medical School, London. Influenced by the late Mr Richard Franklin, he became interested in the surgery of the oesophagus and felt that there was a major place for intubation in the ultimate palliation of oesophageal malignancy. While a registrar at the Royal Postgraduate Medical School, London, he devised a tube based on physiological principles. Coming from a family in which three successive generations of males had been victims of duodenal ulceration, he felt a necessity to study this condition and its treatment – hence his interest in the early work on the H₂ receptor antagonists. Now retired, he continues to follow current advances in gastroenterology.

Professor Charles Frederick Code

(1910–77) was Fellow in Physiology and Clinical Medicine at the Mayo Foundation, Rochester, Minnesota, USA, from 1934 to 1937, Assistant Professor (1939), Associate Professor (1942), Professor of Physiology (1946–75), and Assistant Director for Ulcer Research and Education, Wadsworth VA Hospital, Los Angeles, from 1975. Szurszewski J H. (1998) Obituary. Charles F Code. *Neurogastroenterology and Motility* 10: 183–184.

Professor Duncan Colin-Jones

FRCP (b. 1939) was Consultant Physician and Gastroenterologist at Queen Alexandra Hospital, Portsmouth, from 1975 to 1999, and Clinical

Director, Portsmouth Hospital NHS Trust, from 1994 to 1998.

Dr Nelson Coghill

FRCP (1912–2002) trained in Cambridge and London and graduated in 1937. After six years in the Royal Army Medical Corps during the war (mostly in the Middle East), he was appointed to the West Middlesex Hospital where he set up the Gastrointestinal Unit. He was joined in 1966 by Dr James Stewart who contributed greatly to the development of the unit. They later used methods of experiential learning to promote management in a hospital. His main research interests include gastritis, intestinal electrolyte loss and gastroduodenal haemorrhage. See Stewart J. (2002) Nelson Fuller Coghill. *British Medical Journal* 324: 1399.

Dr Gerard Crean

FRCPEd (b. 1927) was Honorary Consultant Physician at the Western General Hospital, Edinburgh (1959–67), Consultant Physician at the Southern General Hospital, Glasgow (1967–92), and Director of the Diagnostic Methodology Research Unit (1974–92).

Dr Booth Danesh

FRCP (b. 1942) graduated in 1963, and trained in Edinburgh Western General, Glasgow Teaching Hospitals, Middlesex and St Mark's Hospital in London. His research includes the study of gastric and duodenal mucosal damage and protection, and the study of duodenal mucosal microclimate and its response to acid challenge. He has been Consultant Gastroenterologist at Stobhill Hospital, North Glasgow University Hospitals NSH Trust, since 1987.

Professor Graham Dockray

HonFRCP FMedSci (b. 1946) graduated in 1967 from the University of Nottingham and received training in research there. He was appointed to the Department of Physiology at the University of Liverpool in 1970, and is presently Head of Department. In 1973–74, he held a Fogarty International Fellowship in the laboratory of Dr Morton Grossman in Los Angeles, California.

Professor Sir Richard Doll

Kt OBE FRCP FRS (b. 1912) qualified in 1937 from St Thomas' Hospital Medical School, London. He served as a medical officer and physician in the army from 1939 to 1945. In 1946 he joined Sir

Francis Avery Jones and worked with him until 1969, principally as an honorary consultant with a special interest in the treatment of peptic ulcer. From 1948 he worked in Sir Austin Bradford Hill's MRC Statistical Research Unit, becoming its Director in 1961. In 1969 he became Regius Professor of Medicine in Oxford and in 1979 the first Warden of Green College, Oxford. Since 1983 he has worked mostly in an honorary capacity in Sir Richard Peto's Epidemiological Studies Unit in Oxford.

Dr Peter Down

FRCP (b. 1939) graduated in 1963 from St Thomas' Hospital, London. He trained in Portsmouth in nephrology before moving to Dundee to study stool electrolytes. In 1973 he was appointed Physician with an interest in Gastroenterology to the West Dorset Hospital Group and in 1997 was appointed honorary archivist to the British Society of Gastroenterology. He is currently writing a history of British gastroenterology.

Professor Lester Reynold Dragstedt

HonFRCS (1892–1975) qualified from the University of Chicago in 1916 and in 1923 was made Professor of Physiology and Pharmacology in the North Western University Medical School. He researched the treatment of duodenal ulcer, finding that the removal of the duodenum was compatible with life (1918), isolating hormone secreted from the pancreas (1936) and establishing the value of vagotomy (1943). See Anon. (1988) Dragstedt, Lester Reynold. *Lives of the Fellows of the Royal College of Surgeons of England 1974–1982*, 114. See also Desalvo M G, O'Leary J P. (1994) Lester R Dragstedt's contributions to the treatment of peptic ulcer disease. *American Surgeon* **60**: 226–227.

Felicity Edwards

Was research assistant at the West Middlesex Hospital, Isleworth, Middlesex. op cit. note 102.

Mr Harold Edwards

CBE FRCS FRCOG HonFACS (1889–1989) qualified from King's College Hospital, London, in 1923 and was appointed honorary surgeon in 1928, Dean of the Medical School from 1947 to 1950, Director of the Department of Surgery from 1956 to 1970, Hunterian Professor in 1934. He was President of the British Society of Gastroenterology (1961) and of the Association of Surgeons of Great

Britain and Ireland (1971). See Lyle I, Taylor S. (1995) Harold Clifford Edwards. *Lives of the Fellows of the Royal College of Surgeons of England 1983–1990*. London: The Royal College of Surgeons of England, 107–108.

Professor Charles Fletcher

CBE FRCP FFPHM FRS (1911–95) was Physician to Hammersmith Hospital (1952–76), Professor of Clinical Epidemiology, Royal Postgraduate Medical School (1973–76) (Reader from 1952 to 1973), later Professor Emeritus. He was Director of the Medical Research Council Pneumoconiosis Research Unit (1945–52) and Secretary, Medical Research Council Committee on Bronchitis Research (1954–76), Secretary, Committee on Smoking and Health, Royal College of Physicians (1961–71). See Lock S P, Reynolds L A, Tansey E M. (eds) (1998) *Ashes to Ashes: The history of smoking and health*. Amsterdam: Rodopi B V, in particular, pages 148–9, 195, 202–7. See also Scadding J G. (2000) Charles Fletcher. *Munk's Roll* **10**: 146–148. Ness A R, Reynolds L A, Tansey E M. (eds) (2002) op. cit. note 255, 3–36, 89–106.

Professor Sir Patrick Forrest

Kt FRCS FRCPEd FRSEd (b. 1923) graduated from St Andrews University in 1945. Following service as a medical officer with the Royal Navy, he trained in surgery, spending a year as a Mayo Foundation Fellow in Rochester, Minnesota, with Dr Charles Code, which stimulated his interest in gastric secretion. He joined Sir Charles Illingworth's department in Glasgow in 1955, and in 1962 was appointed to the Chair of Surgery in the Welsh National School of Medicine, Cardiff. In 1971 he became Regius Professor of Clinical Surgery in the University of Edinburgh and was, for a time, part-time Chief Scientist to the Department of Home and Health in Scotland. In Edinburgh his interests concentrated on clinical and hormonal aspects of breast cancer. He was Chairman of the Working Group advising the UK Departments of Health on the implementation of the NHS Programme on Breast Screening.

Dr John Fry

CBE FRCS FRCGP (1922–94) qualified in 1944 from Guy's Medical School, London, worked as a GP in Beckenham, Kent, from 1947 to 1991. He served on the Council of the Royal College of General Practitioners (1954–90) and General Medical Council (1970–92). See Fry, John. (2000) *Lives of the Fellows of the Royal College of Surgeons of England 1991–1996*, 104.

Dr Hugh Gainsborough

FRCP (1893–1980) was Consulting Physician to St George's Hospital, London, from 1959, and Director of the Medical Unit, St George's Hospital Medical School. See Hunter M I A. (1984) Hugh Gainsborough. *Munk's Roll 7*: 197–199.

Dr Alan Morton Gill

CBE FRCP (1909–85) was appointed Physician to the West London Hospital in 1939 and later built up a Department of Gastroenterology there. He was a pioneer in the field of gastroscopy and designed his own gastroscope. See Parsons-Smith B G. (1989) Alan Morton Gill. *Munk's Roll 8*: 185–186.

Sir Gordon Gordon-Taylor

CB KBE OBE FRCS HonFRACS HonFRCS HonFRCSI HonFFARCS (1878–1960) qualified from the Middlesex Hospital, London, in 1903 and was appointed Assistant Surgeon in 1920. His many appointments included Vice-President (1941–43) of the Royal College of Surgeons of England, President of the Royal Society of Medicine (1944–46), and President of the Association of Surgeons, Great Britain and Ireland (1944–45). Published works include *The Dramatic in Surgery* (1930) and *The Abdominal Injuries of Warfare* (1939). See Robinson R H O B, Le Fanu W R. (1970) Gordon-Taylor, Sir Gordon. *Lives of the Fellows of the Royal College of Surgeons of England, 1952–1964*. Edinburgh, London: E & S Livingstone, 157–161.

Professor Roderic Gregory

CBE FRS FRCP (1913–90) was Professor of Physiology, University of Liverpool, from 1948 to 1981, later Emeritus. His work focused on the chemistry of gastrin. See, for example, Agarwal K L, Beacham J, Bentley P H, Gregory R A, Kenner G W, Sheppard R C, Tracy H J. (1968) Isolation, structure and synthesis of ovine and bovine gastrins. *Nature* 219: 614–615. See also Dockray G J. (1998) Roderic Alfred Gregory. *Biographical Memoirs of Fellows of the Royal Society* 44: 205–216.

Professor Stewart Goodwin

FRCPATH FRCPA (b. 1932) worked on kidney infection and mycoplasmas in Portsmouth Public Health Laboratory (1969–71), on antibiotics and bacterial virulence in Northwick Park Hospital, Harrow (1971–75), and also in Royal Perth Hospital, Western Australia (1976–89), where his Microbiology Department staff were the first to culture *Helicobacter pylori* in April 1982. He discovered how to grow *H. pylori* in liquid media, and published the first reports of *H. pylori* plasmids, *H. pylori* genomic variation, and the first reliable test for *H. pylori* antibody. He studied five fundamental features of *H. pylori* (ultrastructure, cellular fatty acids, menaquinones, growth characteristics and enzyme capabilities) that provided sufficient justification for a new genus that he named *Helicobacter* in 1989 (op. cit. note 245). He is now Visiting Professor in Microbiology in the Department of Gastroenterology at St George's Hospital Medical School, London.

Professor Morton Grossman

FRCP (1919–81) became Chief of Gastroenterology at the Wadsworth VA Medical Center in Los Angeles in 1955 and in 1974 he became Director of the Center for Ulcer Research and Education (CURE). His main research interests have been in the secretory mechanisms of the stomach and pancreas and the actions of regulatory gastrointestinal peptides. He was Chairman of the Editorial Board of the *Journal of Gastroenterology* from 1973 to 1978 and in 1979 was presented the Friedenwald Medal from the American Gastroenterological Association. See Gregory R A. (1984) Morton Grossman. *Munk's Roll 7*: 231–232.

Dr Jean Guy

FRCR (b. 1941) graduated in 1966 and trained in Cambridge, London and Cardiff. She worked as Consultant Radiologist in south Wales, Somerset, west Wales and is currently in Suffolk. She has been researching the early history of diagnostic radiology in Britain for the past 20 years.

Sir Austin Bradford Hill

Kt CBE FRS (1897–1991) was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine from 1945 until his retirement in 1961. His series of 17 articles in the *Lancet* in 1937 introduced the medical researcher to the use of statistics (reprinted as Principles of Medical Statistics. London: The Lancet, 1937). He was

made an Honorary Fellow of the Royal College of Physicians in 1963. See Doll R. (1994) Austin Bradford Hill. *Biographical Memoirs of Fellows of the Royal Society* 40: 129–140.

Professor Michael Hobsley

FRCS (b. 1929) was Professor of Surgery, London University (1983–94) and Head of the Department of Surgery at Middlesex Hospital Medical School, then University College and Middlesex School of Medicine, London. He was David Patey Professor (1984–94), Emeritus since 1994. His main research interests have been the measurement of gastric acid secretion, surgical operations for reducing gastric secretion, and the relationship of secretion with the aetiology and cure of peptic ulceration. He was President of the British Society of Gastroenterology from 1992 to 1993.

Professor Harold Hopkins

FRS HonFRCS HonFRCP HonFRSM (1918–94) was Professor of Applied Optics at Reading University from 1967 to 1984, then Emeritus, and Head of the Department of Physics, from 1977 to 1980. In the early 1950s he showed that an image could be projected along a bundle of optical fibres, thus making possible a flexible endoscope. He also improved the optics of rigid endoscopes with his rod-lens system. See McCombie C W, Smith J C. (1998) Harold Horace Hopkins. *Biographical Memoirs of Fellows of the Royal Society* 44: 237–252.

Professor Jack Naylor Hunt

FRCP (1917–86) worked in the Department of Physiology, Guy's Hospital Medical School, London, from 1945 to 1976, Professor of Physiology there, from 1962 to 1976. He became Professor of Physiology at Baylor College of Medicine, Houston, Texas, in 1977. See Wolstenholme G, Luniewska V. (1989) Jack Naylor Hunt. *Munk's Roll* 8: 233–234.

Dr Peter Hunter

(b. 1938) qualified from Middlesex Hospital, London, in 1963 and was Consultant Physician at the Royal Shrewsbury Hospital, specializing in endocrinology, from 1974 to 1993. From 1994 to 1997 he read pharmacology at King's College London, as preparation for research on the history of drug discovery in the modern era.

Sir Arthur Hurst (né Hertz)

Kt FRCP (1879–1944) was Consulting Physician and Governor of Guy's Hospital and Medical School, London, and President of the International Society of Gastroenterology. See Anonymous. (1955) Sir Arthur Frederick Hurst. *Munk's Roll* 4: 509–510. Hunt T. (ed.) (1969) op. cit. note 49.

Sir Charles Illingworth

Kt CBE ChM HonFRCS HonFACS (1899–1991) was Regius Professor of Surgery in the University of Glasgow from 1939 to 1964 and Surgeon to the Queen, from 1961 to 1965. In 1963 he received the Lister Medal for his work on peptic ulcers and on the endocrine aspects of the treatment of cancer. See Blandy J, Craig C. (2000) Illingworth, Sir Charles Frederick William. *Lives of the Fellows of the Royal College of Surgeons of England, 1991–1996*. London: Royal College of Surgeons of England, 153–154. See also Sir Charles Illingworth. *The Times*, 26 February 1991.

Professor Roger Jones

FRCP FRCGP FMedSci (b. 1948) trained at Oxford and St Thomas', London, and after hospital, Slough, Berks, jobs in renal and diabetic medicine became a GP in Hampshire in 1979. He set up one of the first open-access endoscopy services for GPs and has been active in clinical and epidemiological research into gastrointestinal disorders since that time. He is currently Wolfson Professor of General Practice at Guy's, King's and St Thomas' School of Medicine, London. He is the founding President of the Primary Care Society for Gastroenterology and the founding Chairman of the European Society for Primary Care Gastroenterology.

Dr Belinda Johnston

(b. 1957) has been Research Fellow at the Lady Sobell Gastrointestinal Unit, Wexham Park Hospital, Slough, Berks, since 1984. Her main interests are in *Helicobacter pylori* and its role in upper gastrointestinal disease, its detection and eradication. She set up and runs an open-access ¹³C-urea breath test service for the non-invasive detection of *H. pylori* and has done much work on developing the breath test in order for a product licence to be granted.

Dr Horace Joules

FRCP (1902–1977) was Physician and Medical Director, Central Middlesex Hospital, London, from 1935 to 1965. See Ball K P. (1984) Horace Joules. *Munk's Roll* 7: 307–309.

Sir Andrew Kay

FRCS FRCSed FRFPPSG FRSEd (b. 1916) was Regius Professor of Surgery, University of Glasgow, from 1964 to 1981 and part time Chief Scientist, Scottish Home and Health Department, from 1973 to 1981.

Professor George Kenner

FRS (1922–1978) was Heath Harrison Professor of Organic Chemistry at University of Liverpool from 1957 to 1976 and Royal Society Research Professor, University of Liverpool, from 1977. See Lord Todd. (1979) George Wallace Kenner. *Biographical Memoirs of Fellows of the Royal Society* 25: 391–420.

Mr Raymond (Jerry) Kirk

FRCS FRSM (b. 1923) was Consultant Surgeon at the Willesden General Hospital from 1962 to 1974, Royal Free Hospital Group, from 1964 to 1989. He has been Honorary Consulting Surgeon at the Royal Free Hospital, London, since 1989, Honorary Senior Lecturer in Surgery and part-time Lecturer in Anatomy, Royal Free and University College Medical School, Royal Free Campus (formerly Royal Free Hospital School of Medicine), London, since 1989.

Professor Michael Langman

FRCP FMedSci (b. 1935) was William Withering Professor of Medicine at the University of Birmingham Medical School from 1987 to 2000, Dean from 1992 to 1997 and has been Honorary Professor of Medicine since 2000. He was President of the British Society of Gastroenterology from 1997 to 1999.

Professor John Lennard-Jones

FRCP FRCS (b. 1927) graduated in 1953, having trained in Cambridge and at University College Medical School in London. From 1958 to 1974, he was closely associated with the Central Middlesex Hospital, as registrar, senior registrar, and latterly as a member of the MRC Gastroenterology Research Unit. During this time, and while acting as registrar in the MRC Department of Clinical Research at UCH, he studied patients with duodenal ulcer. In 1965, he was appointed to the Consultant Staff at UCH and in 1974, moved to the Royal London

Hospital, first as Reader, and then as Professor of Gastroenterology. From 1965 to 1992 he was also Consultant Gastroenterologist at St Mark's Hospital, London.

Dr Jonathan Levi

FRCP (1933–99) was Consultant Physician and Gastroenterologist at Northwick Park and St Mark's Hospitals, London, from 1969 to 1997. As Nuffield Fellow in New York he discovered two important cytoplasmic proteins involved in bilirubin and drug transfer. See Collins I. (1999) The good doctor of life. *Guardian*, February 6, page 21.

Dr Robert Logan

FRCP (b. 1959) was a research fellow at St Mary's and Central Middlesex Hospitals, London, from 1989–94 with Dr Hugh Baron and Dr George Misiewicz. He was subsequently a Wellcome Fellow in Nottingham with Professors Peter Boriello and Chris Hawkey until 1999. His published works are on the development of the urea breath test for the detection of *H. pylori* and its application to further understanding of the epidemiology, pathogenesis and treatment of *H. pylori* infection.

Professor Marshall Marinker

(b. 1930) was in general practice in Middlesex and Essex from 1959 to 1973 and Foundation Professor of Community Health (later General Practice) and Head of the Department of Community Health at the University of Leicester from 1974 until 1982. He has been Visiting Professor at the Department of General Practice, United Medical and Dental Schools of Guy's and St Thomas' Hospitals, since 1991.

Professor Barry Marshall

FRS FRACP (b. 1951) has been Professor of Microbiology, University of Western Australia, since 2000. His published works include *Campylobacter pylori* (1988) and *Helicobacter pylori in Peptic Ulceration and Gastritis* (1991). op. cit. notes 40, 231, 239 and 244.

Professor Kenneth McColl

(b. 1950) graduated in 1974 and completed his training in internal medicine and gastroenterology in Glasgow. He spent a year in San Francisco as part of an MRC Travelling Fellowship. He was appointed Consultant Physician and Gastroenterologist in the Department of Medicine and Therapeutics, Western Infirmary, Glasgow in 1984. In 1992 he was appointed Professor of Gastroenterology in the

University of Glasgow. His special interests largely focus on the pathophysiology of upper gastrointestinal disease and its relevance to diagnosis and treatment, and include peptic ulcer disease, *H. pylori* infection and gastric and oesophageal cancer. See McColl K E L. (1999) *Helicobacter pylori* 1988–1998. *European Journal of Gastroenterology and Hepatology* 11: 13–16.

Sir Godfrey Milton-Thompson

KBE FRCP (b. 1930) was Honorary Research Fellow, St Mark's Hospital, London, from 1969 to 1971, Professor of Naval Medicine (1975–80), Deputy Medical Director General (Naval), (1982–84). He has been Vice-President of the British Digestive Foundation since 1993 and has published widely on clinical pharmacology of the gastrointestinal tract and therapy of peptic ulcer. See, for example, Milton-Thompson G J. (1974) The problem of duodenal ulcer in the Royal Navy. *Journal of the Royal Navy Medical Services* 60: 45–48. *idem* (1977) The use and abuse of histamine H₂-receptor antagonists. *ibid.* 63: 9–14. Hunt R H, Milton-Thompson G J. (1980) The epidemiology and pathogenesis of gastric ulcer. *Frontiers of Gastrointestinal Research* 6: 57–70. See also op. cit. note 126.

Dr George Misiewicz

FRCP (b. 1930) qualified from St Bartholomew's Hospital, London, in 1956 and trained in gastroenterology in the MRC Gastroenterology Research Unit and in the Department of Gastroenterology at the Central Middlesex Hospital, London, under Sir Francis Avery Jones. His research began in motility of the gut, but he then became interested in acid secretion and *Helicobacter pylori*. He has been Secretary and President of the British Society of Gastroenterology (1983–88), Editor of *Gut* (1980–87) and Editor of the *European Journal of Gastroenterology and Hepatology* since 1989.

Professor Berkeley Moynihan

First Baron Moynihan since 1929 KCMG CB FRCS (1865–1936) was Professor of Clinical Surgery at Leeds from 1906 to 1926. His published works include *Abdominal Operations* (1905) and articles on surgical treatment of diseases of the stomach, pancreas, gastric and duodenal ulcers, and gallstones. He was President of the Royal College of Surgeons from 1926 to 1932. See Power D'Arcy,

Le Fanu W R. (1953) Moynihan, Sir Berkeley George Andrew, Lord Moynihan of Leeds. *Lives of the Fellows of the Royal College of Surgeons of England, 1930–1951*. London: Royal College of Surgeons of England, 565–570.

Professor Timothy Northfield

FRCP (b. 1935) was houseman to Sir Christopher Booth at the Hammersmith Hospital, London, registrar in the MRC Gastroenterology Unit at the Central Middlesex Hospital, London, under Sir Francis Avery Jones, and senior registrar under Professor Herman Dowling at Guy's Hospital, London. In 1974 he was appointed Consultant Gastroenterologist at St James' Hospital, Balham. He has carried out many clinical trials on the effects of H₂ receptor antagonists and proton-pump inhibitors on peptic ulcer and was Chairman of the Steering Committee for the National Audit of Acute Gastrointestinal Bleeding. He has taken an active interest in *H. pylori* infection, including the use of *H. pylori* serology and the role of *H. pylori* infection in reducing gastric mucosal defence and in causing coronary heart disease.

Professor Colm Ó'Moráin

FRCPI FRCP FEBG FACG (b. 1946) qualified in Dublin in 1972. He was Clinical Fellow in Nice University between 1975 and 1977, senior registrar at Northwick Park Hospital, Harrow, between 1978 and 1983 and Fogart Fellow of Albert Einstein College of Medicine, Bronx, NY, USA, between 1983 and 1985. He became Associate Professor of Gastroenterology, Trinity College Dublin, Acting Head of Department of Medicine, Adelaide and Meath Hospitals, Dublin, in 1993, and Professor of Medicine at Trinity College Dublin in 2001. His research interests include inflammatory bowel disease, where he pioneered treatment of Crohn's disease with elemental diet, and *H. pylori*. See Buckley M J, O'Morain C A. (1998) *Helicobacter* biology: discovery. *British Medical Bulletin* 54: 7–16.

Dr John Poulley

FRCP (b. 1918) qualified in September 1939 from the Middlesex Hospital Medical School, London. He researched on ulcerative colitis and Crohn's disease. [see, for example, Poulley J W. (1950) Ulcerative colitis: study of 173 cases. *Gastroenterology* 16: 566–576. *idem* (1971) Crohn's disease. Treatment by corticosteroids, antibiotics and psychotherapy. *Psychotherapy*

and *Psychosomatics* 19: 111–117. *idem* (1974) Psychological management of Crohn's disease. *Practitioner* 213: 59–64.

Sir Richard Peto

Kt FRS (b. 1943) was Reader in Cancer Studies, University of Oxford (1975–92) and has been Professor of Medical Statistics and Epidemiology since 1992, and Fellow of Green College, Oxford, since 1979.

Professor Roy Pounder

FRCP (b. 1944) has been Professor of Medicine, Royal Free and University College Medical School, London, since 1992, and Honorary Consultant Physician and Gastroenterologist, Royal Free Hospital, since 1980. He was Secretary of the British Society of Gastroenterology in 1982–4. He trained in gastroenterology under Sir Roy Calne (Addenbrooke's Hospital, Cambridge), Sir Christopher Booth, Professor Hermon Dowling and Dr Graham Neale (Hammersmith Hospital, London), Sir Francis Avery Jones, Drs Donald Kellock and George Misiewicz (Central Middlesex Hospital, London), and Drs Brian Creamer and Richard Thompson (St Thomas' Hospital, London). He is Founding Co-editor of *Alimentary Pharmacology and Therapeutics* (from 1987), Editor-in-Chief, *GastroHep.com* (from 2000) and Clinical Vice-President, Royal College of Physicians of London (2002–04).

Dr Frank Pygott

DPH DMRE (1911–95) was appointed Radiologist at the Central Middlesex Hospital in London and set up the radiological services there. See Avery Jones F. (1995) F Pygott. *British Medical Journal* 311: 626.

Dr Rudolf Schindler

(1888–1968) was Assistant in the Second Medical Department at the Munich-Schwabing Hospital from 1919 to 1924. In 1921 he invented an improved model of the rigid optical gastroscope and in 1924, consulted with George Wolf, on the construction of the flexible gastroscope, which was to become the prototype for many similar instruments. In 1934 he was established as Visiting Professor of Medicine at the University of Chicago, Assistant Professor of Medicine (1937–43). He was then appointed Clinical Professor of Medicine,

College of Medical Evangelists, Los Angeles, and Consultant in Gastroenterology at the Veterans Administration Hospital, in Van Nuys and later Long Beach. See Stempien S J, Dagradi A E. (1969) Dr Rudolf Schindler. *Gastroenterology* 56: 367–369.

Dr Hans Selye

(1907–82) founded the Institute of Experimental Medicine and Surgery at the University of Montreal in 1945 and was Director, from 1945 to 1977. In 1977 he established the International Institute of Stress, Montreal. *op. cit.* note 51.

Professor Robert Steiner

FRCR FRCP CRCS CBE (b. 1918) was Professor of Diagnostic Radiology, University of London, from 1961 to 1983, at the Royal Postgraduate Medical School, Hammersmith Hospital, now Professor Emeritus. He is former Editor of the *British Journal of Radiology*, past President of the British Institute of Radiology and past President of the Royal College of Radiologists.

Dr Tilli Tansey

HonMRCP (b. 1953) is Convenor of the History of Twentieth Century Medicine Group and Reader in the History of Modern Medical Sciences at the Wellcome Trust Centre for the History of Medicine, University College London.

Mr Hermon Taylor

FRCS (1905–2001) was Consultant Surgeon at the London Hospital, working there from 1939 to 1970. His invention of the steering system in the flexible gastroscope is still used in endoscopes today. See Hermon Taylor. (2001) *The Times*, 8 February 2001, 25.

Mr Frank Tovey

OBE ChM FRCS (b. 1921) worked as a surgeon in China and in India for 20 years and from 1968 in Basingstoke. Since 1968 he has been an Honorary Research Fellow in the Department of Surgery at University College Hospital, London, and then at the Royal Free and University College London Medical School, London. His interests include surgery of duodenal ulcer and its metabolic effects, plus the geographical distribution of duodenal ulcer and its relationship to staple diets. This led to experimental work into the nature of protective factors and ulcerogenic factors in diets.

Lord Turnberg of Cheadle

Kt FRCP FRCS (b. 1934) was Professor of Medicine, University of Manchester, from 1973 to 1997, President of the Royal College of Physicians from 1992 to 1997, and Chairman, Public Health Laboratory Health Board, since 1997. See Christie D A, Tansey E M. (eds) (2000) Intestinal absorption. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 8. London: The Wellcome Trust.

Dr David Tyrrell

CBE FRCP FRCPATH FRS (b. 1925) trained in Sheffield and New York and then worked for the Medical Research Council, mainly at the Common Cold Unit, Salisbury, and was Deputy Director of the Clinical Research Centre, Northwick Park. He was involved in studies of the cause and prevention of acute respiratory diseases and other infections.

Dr Owen Wangenstein

HonFRCS FACS HonFRCSI (1885–1981) was Head of the Department of Surgery at the University of Minnesota from 1929 to 1967. The well-known ‘Wangensteen tube’ facilitates management of bowel obstruction with suction applied to an indwelling duodenal tube, and he has made many contributions in the treatment of stomach cancer. See, for example, Wangenstein O H, Wangenstein S D. (1977) History of gastric surgery: glimpses into its early and more recent past, in Nyhus L M, Wastell C. (eds) *Surgery of the Stomach and Duodenum*, 3rd edn. Boston: Little, Brown and Company, 3–39. See Cornelius E H, Taylor S F. (1988) Wangenstein,

Owen Harding. *Lives of the Fellows of the Royal College of Surgeons of England, 1974–1982*. London: Royal College of Surgeons of England, 405–406.

Professor Richard Welbourn

FRCS HonFACS (b. 1919) was Professor of Surgery, University of London, and Director, Department of Surgery, Royal Postgraduate Medical School and Hammersmith Hospital (1963–79), Honorary Consultant Surgeon, Hammersmith Hospital (1979–82), Professor of Surgical Endocrinology, Royal Postgraduate Medical School, University of London (1979–82), now Emeritus.

Dr John Wood

FFPM (b. 1949) directed drug development at Glaxo and Glaxo Wellcome (1983–2001). In particular, he was responsible for more than a decade for the global clinical development of Zantac (ranitidine). His special interests are gastrointestinal pharmacology and therapeutics. He is currently Managing Director of Wood and Mills Ltd, Pharma Consultancy.

Professor John Wyllie

FRCS (b. 1933) was Professor of Surgical Studies at University College London and Honorary Consultant Surgeon at University Hospitals and Whittington Hospital NHS Trusts, with a special interest in oesophageal disease; but had enduring interest in drug action. He worked with the two Nobel Prize winners, Sir James Black and Sir John Vane, and retired in 1997.

GLOSSARY

Agranulocytosis

A disorder in which there is a severe deficiency of neutrophils usually as a result of damage to the bone marrow.

Anticholinergics

A class of drugs that block the activity of acetylcholine at muscarinic receptors (e.g. poldine) and cause a decrease in acid secretion by gastric **parietal cells**.

Ankle oedema

Swelling of the ankles due to salt and water retention.

Antrectomy

An operation in which the lower part of the stomach (the antrum) is removed. See Appendix A.

Barrett's ulcer

An ulcer arising in Barrett's oesophagitis, an area of abnormal mucosa in the lower oesophagus, probably due to chronic reflux of acid.

Burimamide

The first **H₂ receptor antagonist**. See Appendix B, Figure 2.

Carbenoxolone sodium (Biogastrone, Duogastrone)

A drug derived from liquorice that was one of the first to be shown by controlled trial to increase the healing rate of gastric ulcer. Common side-effects include sodium and water retention, and occasionally hypokalaemia (low concentrations of potassium in the blood). These effects may cause or worsen hypertension (high blood pressure) and heart failure.

Cimetidine (Tagamet)

An **H₂ receptor antagonist** – the first to be marketed by Smith Kline & French in 1976. See page 69 and Appendix B, Figure 3.

Denol

See **tripotassium dicitratobismuthate**.

Dumping

A group of symptoms that may occur after a **gastrectomy**. After a meal the patient may feel faint, bloated, weak and nauseated, has a rapid pulse, and may sweat and become pale. The attack is believed to be caused by rapid stomach emptying, leading to the drawing of fluid from the blood into the intestine. Later, the blood sugar may fall and also cause symptoms.

Duogastrone

See **carbenoxolone sodium**.

Enprostil

A synthetic prostaglandin E₂ antagonist that also decreases acid secretion was used in clinical trials for the treatment of gastric and duodenal ulcers but was not marketed.

Enterogastrone

A hormone from the small intestine (duodenum) that inhibits the secretion of gastric juice by the stomach. It is released when the stomach contents pass into the small intestine.

Famotidine (Pepcid)

An **H₂ receptor antagonist**. See Appendix B, Figure 3.

Fistula

An abnormal communication between two hollow organs or between a hollow organ and the exterior.

Gastrectomy

Surgical removal of all or part of the stomach (partial gastrectomy, see **antrectomy**). See Appendix A.

Gastrin

A hormone produced by specialized cells (**G cells**) in the gastric mucosa and stimulates the production of gastric acid.

Gastrinoma

A rare tumour of **G cells** that secrete excess amounts of the hormone **gastrin**, causing the **Zollinger–Ellinson syndrome**.

Gastro-jejunostomy (gastro-enterostomy)

An operation in which an opening was created between the stomach and jejunum as a surgical treatment for peptic ulcer.

G cell

Any of the cells of the mucous membrane of the stomach that are responsible for the production of **gastrin**.

H2 receptor antagonist

A class of drug that competitively inhibits histamine at its receptor, to decrease gastric acid secretion.

Haematemesis

Vomiting of blood characteristically arising from bleeding in the oesophagus, stomach, or duodenum, most frequently due to gastric or duodenal ulceration.

Hypercholesterolaemia

Raised blood cholesterol level.

Hypochondrium

That part of the abdomen below each costal margin.

Hypergastrinaemia

High blood concentrations of the hormone **gastrin**.

Ischaemia

An inadequate flow of blood to a part of the body, caused by constriction or blockage of the blood vessels supplying it.

Leucopaenia

A reduction in the number of white blood cells (leucocytes) in the blood.

Meckel's diverticulum

A small pouch arising from the ileum not far from the ileocaecal valve and containing gastric mucosal cells.

Metaplasia

An abnormal change in the nature of a tissue.

Metiamide

The first **H2 receptor antagonist** to be used in a clinical trial. See Appendix B, Figure 3.

Non-steroidal anti-inflammatory drug (NSAID)

A group of drugs used for pain relief, which act by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2) responsible for controlling the formation of prostaglandins, important mediators of inflammation. Adverse effects include gastric bleeding and ulceration.

Omeprazole

The first **proton-pump inhibitor**.

Pangastritis

Inflammation (gastritis) of the entire stomach lining.

Parietal cells

Cells in the stomach wall that make hydrochloric acid.

Pepcid

See **Famotidine**.

Peritonitis

Inflammation of the peritoneum.

Poldine (Nacton)

An anticholinergic drug, similar to atropine, which inhibits gastric secretion, and was used to treat gastric and duodenal ulcers.

Proton-pump inhibitor (PPI)

A class of drug that blocks the enzyme H^+ , K^+ ATPase to cause profound inhibition of gastric acid secretion (see **omeprazole**).

Pyloric stenosis

A narrowing of the outlet of the stomach (pylorus) that causes delay in passage of the stomach contents to the duodenum, leading to repeated vomiting. It is often caused by a peptic ulcer close to the pylorus.

Pylorid

See **ranitidine bismuth citrate**.

Pyloroplasty

An operation in which the outlet of the stomach (pylorus) is widened. It is done to allow the contents of the stomach to pass more easily into the duodenum, particularly after **vagotomy** to treat peptic ulcers (which would otherwise cause delay in gastric emptying). See Appendix A.

Pyrogastrone

A proprietary combination of **carbenoxolone sodium**, magnesium silicate, dried aluminium hydroxide and sodium bicarbonate, and alginic acid, used for the treatment of oesophagitis and oesophageal ulcers.

Ranitidine (Zantac)

An **H₂ receptor antagonist** (Glaxo Wellcome), see Appendix B, Figure 3.

Ranitidine bismuth citrate (Pylorid)

An **H₂ receptor antagonist** containing bismuth, used as an adjunct to antibiotics (clarithromycin and amoxicillin or metronidazole) for the eradication of *Helicobacter pylori*.

Secretagogue

A drug or chemical that promotes or stimulates secretion.

Sucralfate (Antepsin)

An aluminium-containing drug that forms a protective coating over the stomach or duodenal lining, used in the treatment of peptic ulcer.

Tagamet

See **cimetidine**.

Tripotassium dicitratobismuthate (Denol)

A bismuth-containing drug used to treat peptic ulceration.

Truncal vagotomy

See **vagotomy**.

Urease

The enzyme that catalyses the hydrolysis of urea to ammonia and carbon dioxide.

Urogastrone

A circulating gut hormone that inhibits the effects of pentagastrin.

Vagotomy

The surgical cutting of any of the branches of the vagus nerve, usually performed to reduce secretion of acid and pepsin by the stomach in order to cure a peptic ulcer. **Truncal vagotomy** is the cutting of the main trunks of the vagus nerve. See Appendix A.

Zantac

See **ranitidine**.

Zollinger–Ellison syndrome

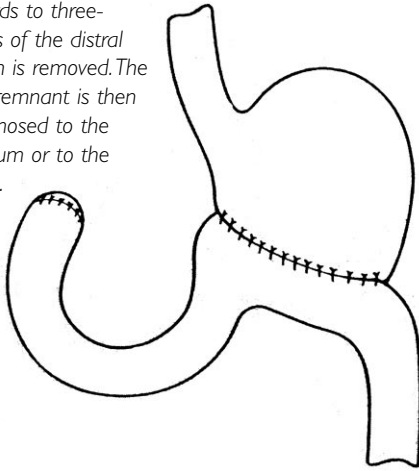
Characterized by persistent basal gastric acid hypersecretion due to **hypergastrinaemia** of tumour origin. Clinical problems associated with the condition include peptic ulcer, and oesophagitis.

APPENDIX A

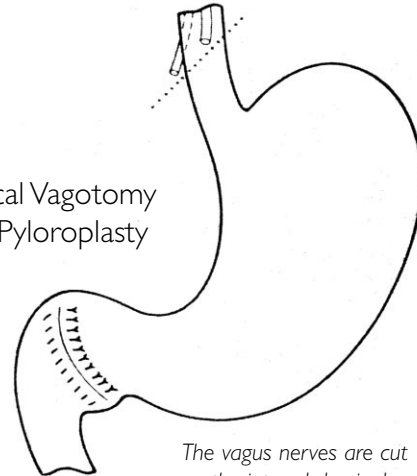
Surgical Procedures

Partial Gastrectomy

Two-thirds to three-quarters of the distal stomach is removed. The gastric remnant is then anastomosed to the duodenum or to the jejunum.

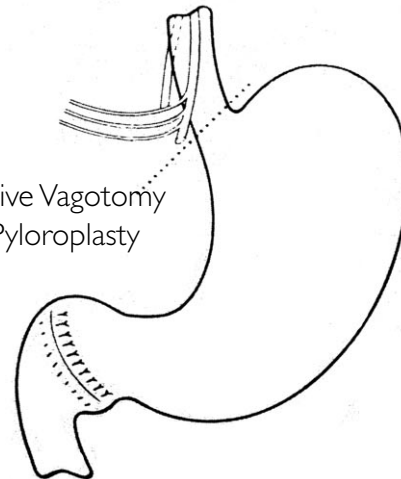


Truncal Vagotomy with Pyloroplasty

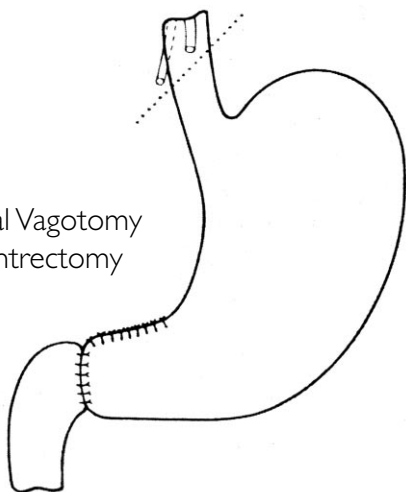


The vagus nerves are cut on the intra-abdominal portion of the oesophagus. Drainage is provided by either a pyloroplasty or a gastroenterostomy.

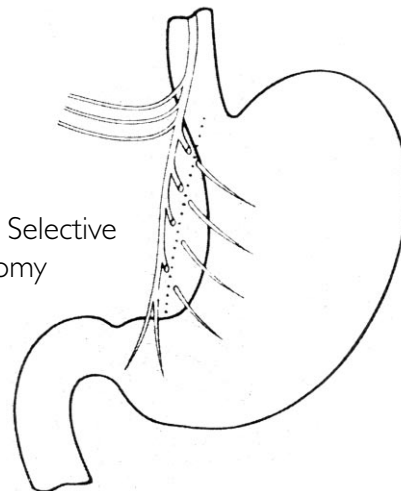
Selective Vagotomy with Pyloroplasty



Truncal Vagotomy and Antrectomy



Highly Selective Vagotomy



APPENDIX B

Chemical Structures

Figure 1. Histamine leading to 2-methylhistamine and 4-methylhistamine (see page 66). *op. cit.* note 161.

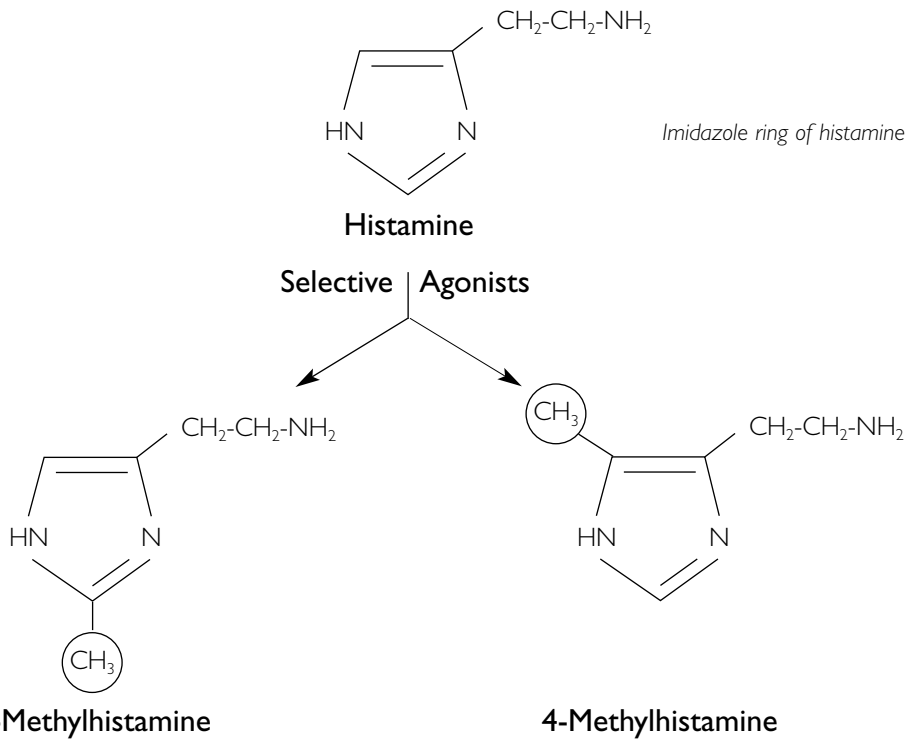


Figure 1a: H_1 -receptor agonist

Figure 1b: H_2 -receptor agonist

Figure 2. From histamine to burimamide (see page 68). Modification of side chain. *op. cit.* note 161.

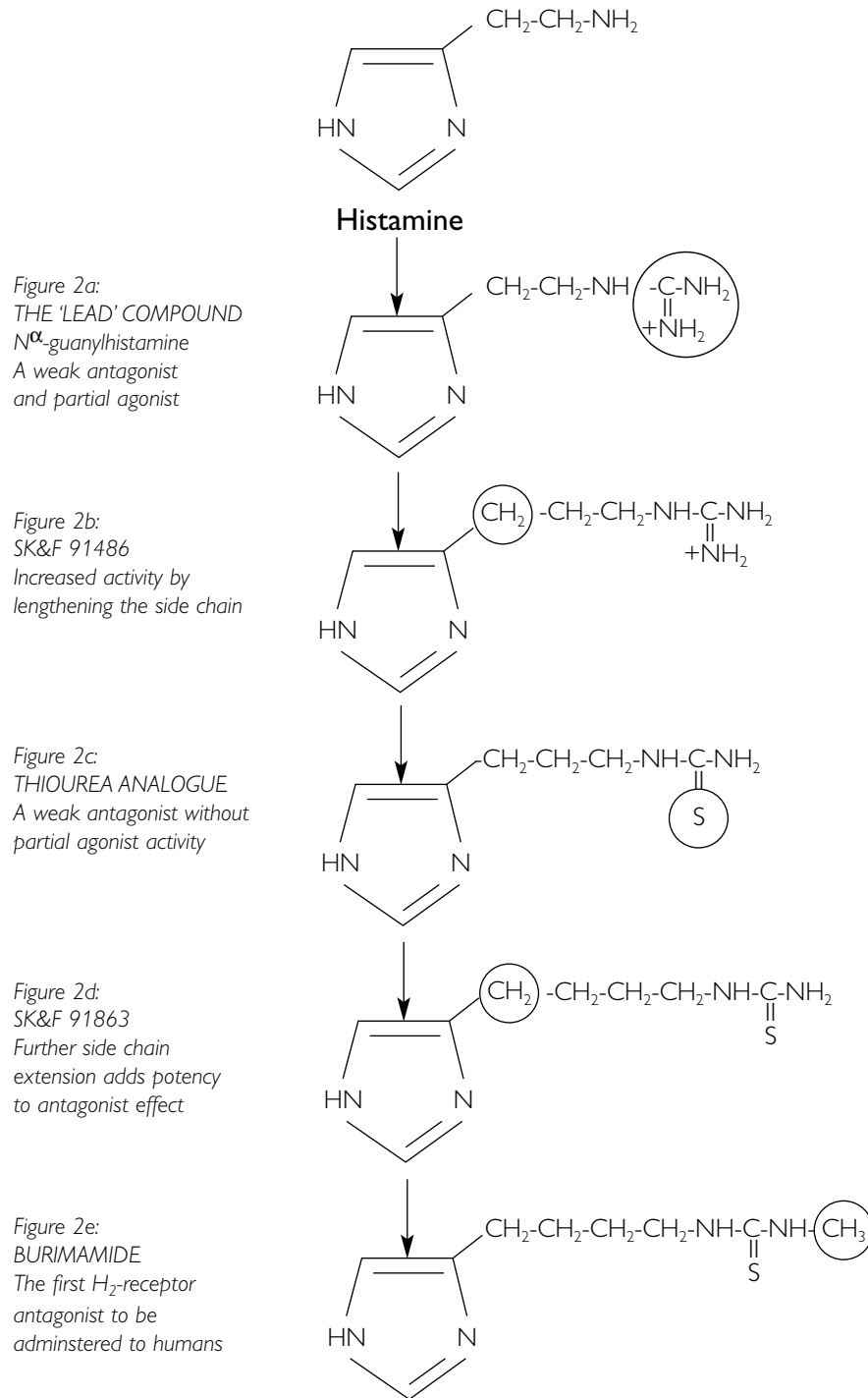
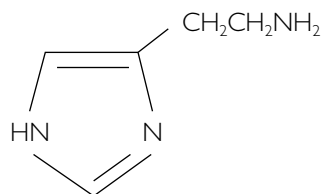
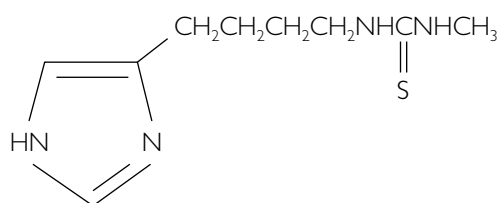


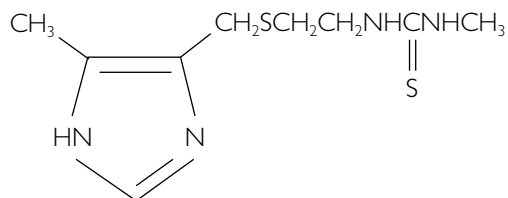
Figure 3. Chemical structures of some H₂ receptor antagonists.



Histamine

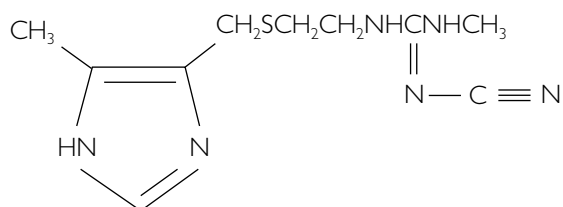


Burimamide



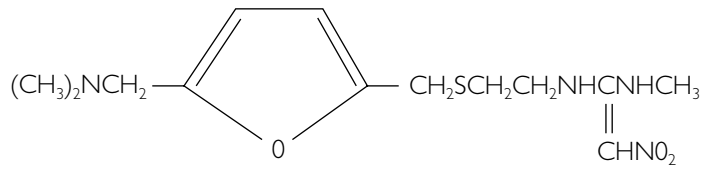
Metiamide

*Thiourea group replaced
with cyanoguanidine group*

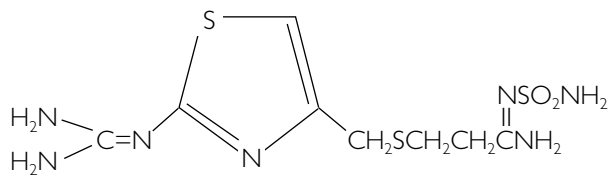


Cimetidine
(Tagamet, SK&F)

H₂ receptor antagonists (continued)



**Ranitidine (Zantac,
Glaxo Wellcome)**



Famotidine (Pepcid)

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